THE CONTRIBUTION OF SEROTONIN 2A RECEPTORS TO THE EMOTIONAL AND VISUAL EFFECTS OF PSILOCYBIN

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Abstract

Converging evidence from neuroimaging, pharmacological and molecular studies suggests that serotonin 2A (5-HT2A) and 1A (5-HT1A) subreceptors are involved in the pathophysiology of negative emotional processing biases in affective disorders. This view is supported by the finding that 5-HT1A and 5-HT2A receptor densities are altered in prefrontal and limbic regions in patients with depression and anxiety disorders. Furthermore, 5-HT1A receptor agonists are effective at enhancing the antidepressant effect of selective serotonin reuptake inhibitors, and preferential 5-HT2A receptor agonists exhibit anxiolytic and antidepressant effects in animal models of affective disorders. The hallucinogen psilocybin, which activates 5-H2A and 1A receptors, was recently found to acutely enhances mood in healthy subjects and to reduce depression and anxiety symptoms in terminal cancer patients. However, the effect of psilocybin on the emotional processing biases across different psychological domains, and the specific contribution of 5-HT2A receptor activation, remain unknown.

In addition, the 5-HT2A and 1A receptors are highly expressed in visual pathways and aberrant 5-HT2A receptor expression has been associated with the formation of visual hallucinations in Parkinson's disease and schizophrenia. Furthermore, activation of 5-HT2A receptors is thought to be predominantly responsible for psilocybin-induced visual hallucinations. However, the neurophysiological mechanisms that mediate between 5-HT2A receptor activation and the formation of visual hallucinations in psilocybin-induced and pathological states remain undefined.

To clarify these issues further, we assessed in the first study (Chapter 2) the effects of psilocybin (215 µg/kg vs. placebo) on emotional processing bias in face recognition, goal-directed behaviour and mood states in 17 healthy subjects. To disentangle the specific contribution of 5-HT2A receptors, subjects were pretreated with the preferential 5-HT2A receptor antagonist ketanserin (50 mg vs. placebo). Psilocybin biased emotional processing towards positive information across different psychological domains. Specifically, psilocybin enhanced positive mood states and disrupted the recognition of negative facial expressions. Furthermore, psilocybin increased goal-directed behaviour towards positive cues, facilitated positive but inhibited negative sequential emotional effects, and more strongly decreased the P300 potential for negative and neutral stimuli than for positive stimuli. Ketanserin selectively blocked the psilocybin-induced mood enhancement and the disruption in the recognition of negative facial expression, indicating that 5-HT2A receptor activation mediates these psilocybin-induced effects.

In the second study (Chapter 3), we assessed the effects of two doses of psilocybin (125 and 250 µg/kg vs. placebo) on the spatiotemporal dynamics of visual modal object completion in 17 healthy subjects using visual-evoked potential recordings in conjunction with topographic mapping and sLORETA source analysis. These physiological effects were related to the subjective

intensity of psilocybin-induced visual hallucinations, as quantified by psychometric measurement. Psilocybin elicited a dose-dependent increase in the medial P1 potential, reflecting amplified activity in early visual areas. By contrast, there was a strong dose-dependent decrease in the N170 potential, which was most apparent during the processing of incomplete object figures and therefore indicates aberrant modal object completion. The overall reduction in activity of the right extrastriate and posterior parietal areas during the period of the N170 potential was further positively correlated with the intensity of visual hallucinations.

It is possible that 5-HT2A receptor activation mediates the psilocybin-induced effects on the visual evoked potential during modal object completion and additionally increases the excitability of the visual cortex which, in turn, underlies the psilocybin-induced visual hallucinations. This hypothesis was tested in the third study (Chapter 4). Specifically, we assessed the effect of psilocybin (215 µg/kg vs. placebo) on the alpha oscillations that regulate cortical excitability and on the early visual-evoked potentials (P1 and N170) in 15 healthy subjects. To delineate the specific contribution of 5-HT2A receptors, subjects were pretreated with ketanserin (50 mg vs. placebo). Psilocybin selectively increased the medial P1 potential, confirming the results of study two, and ketanserin selectively decreased the P1 potential over the same electrode sites. The subsequent N170 potential was decreased by psilocybin and associated with perceptual alterations. Both the N170 potential and the perceptual alterations were blocked by ketanserin, which suggests that the reduction of the N170 potential may underlie 5-HT2A receptor-mediated visual hallucinations. Finally, psilocybin strongly decreased the prestimulus alpha power and blocked the stimulus-induced alpha desynchronization, and both of these effects were reversed by ketanserin. This suggests that 5-HT2A receptor activation induces a processing mode in which stimulus-driven excitation is overwhelmed by spontaneously patterned neuronal excitation.

Taken together, these findings indicate that psilocybin markedly modulates conscious, behavioural and neurophysiological indices of visual and emotional processing through 5-HT2A receptor activation. The identified effect of 5-HT2A receptor activation on the emotional processing bias provides a potential mechanism for the pathophysiology of dysfunctional emotional biases in depression, thereby providing a framework to test the putative antidepressant effects of psilocybin and related substances in affective disorders. Furthermore, the present studies revealed several 5-HT2A dependent neurophysiological mechanisms underlying aberrant visual processing. A reduction in the N170 potential was identified as a key process in 5-HT2A receptor-mediated visual hallucinations and aberrant object completion that may not be implicated only in psilocybin-induced states, but also in the pathophysiology of hallucinations in schizophrenia and Parkinson’s disease.

Zusammenfassung

Konvergierende Befunde von bildgebenden, pharmakologischen und molekularen Studien weisen darauf hin, dass die serotonergen 2A (5-HT2A) und 1A (5-HT1A) Subrezeptoren eine zentrale Rolle in der Pathophysiologie von negativen emotionalen Verarbeitungstendenzen in affektiven Erkrankungen spielen. Diese Sichtweise basiert einerseits auf dem Befund, dass depressive Patienten sowie Angstpatienten eine veränderte Dichte von 5-HT2A und 1A Rezeptoren innerhalb präfrontaler und limischer Regionen aufweisen. Des Weiteren verstärkt die kombinierte Gabe von 5-HT1A Rezeptor Agonisten die antidepressive Wirkung von SSRIs und präferentielle 5-HT2A Rezeptor Agonisten zeigen antidepressive und angstlösende Wirkungen in verschiedenen Tiermodellen von Emotionserkrankungen. Das Halluzinogen Psilocybin stimuliert 5-HT2A und 1A Rezeptoren und führte in kürzlich veröffentlichten Studien zu einer akuten Stimmungsaufhellung bei gesunden Probanden und zu einer Reduktion von Depressions- und Angstsymptome bei Krebspatienten. Die Effekte von Psilocybin auf die emotionalen Verarbeitungstendenzen in verschiedenen psychologischen Domänen, sowie der spezifische Beitrag der 5-HT2A Rezeptoraktivierung, bleiben jedoch unbekannt.

Die 5-HT2A und 1A Rezeptoren werden des Weiteren mit einer hohen Dichte in visuellen kortikalen Verarbeitungsstrecken exprimiert, und Veränderungen der Expression wurden kürzlich mit der Entstehung von visuellen Halluzinationen bei Parkinson und Schizophrenie Patienten in Verbindung gebracht. Ferner unterliegt die Aktivierung von 5-HT2A Rezeptoren wahrscheinlich den Psilocybin-induzierten visuellen Halluzinationen. Dennoch sind die neuophysiologischen Mechanismen, welche zwischen der Aktivierung von 5-HT2A Rezeptoren und der Bildung von visuellen Halluzinationen vermitteln, weitgehend unbekannt.

Um diese offenen Fragen zu klären, wurden in der ersten Studie (Kapitel 2) die Effekte von Psilocybin (215 µg/kg vs. Placebo) auf die Stimmung und die emotionalen Verarbeitungstendenzen in der Gesichtswahrnehmung sowie dem zielgerichteten Verhalten bei 17 gesunden Probanden untersucht. Um den spezifischen Beitrag des 5-HT2A Rezeptors zu isolieren, wurde den Probanden zusätzlich der präferenzielle 5-HT2A Rezeptor Antagonist Ketanserin (50 mg vs. Placebo) verabreicht. Die Befunde ergaben, dass Psilocybin über verschiedene psychologische Domänen konsistent eine präferenzielle Verarbeitung von positiven im Vergleich zu negativen Emotionen induzierte. D.h. Psilocybin löste positive Gefühlszustände aus und beeinträchtigte die Erkennung von negativen Gesichtsausdrücken. Psilocybin führte des Weiteren zu einer Verschiebung des zielgerichteten Verhaltens hin zu positiven Emotionen, förderte die positiven nicht aber die negativen sequentiellen emotionalen Effekte, und reduzierte das P300 Potential stärker auf negative und neutrale Reize im Vergleich zu positiven Reizen. Ein zentraler Beitrag des 5-HT2A Rezeptors in der Vermittlung der Psilocybin-induzierten positiven Gefühlzuständen sowie der

reduzierten Erkennung von negativen Gesichtsausdrücken ist dadurch ersichtlich, dass Ketanserin diese Psilocybin-induzierte Effekte blockierte.

In der zweiten Studie (Kapitel 3) wurden die Effekte von zwei Dosen Psilocybin (125 und 250 µg/kg vs. Placebo) auf die räumlich-zeitliche Dynamik der visuellen modalen Objektvervollständigung bei 17 gesunden Probanden mittels der Aufzeichnung von visuell evozierten Potentialen in Verbindung mit topographischer Analyse und sLORETA Quellenschätzung untersucht. Diese physiologischen Effekte wurden anschliessend in Bezug zur psychometrisch quantifizierter Intensität von visuellen Halluzinationen gesetzt. Psilocybin erhöhte dosisabhängig das mediale P1 Potential, was eine verstärkte Aktivierung in frühen visuellen Arealen wiederspiegelte. Im Gegensatz dazu wurde das N170 Potential dosisabhängig reduziert, was für unvollständige Figuren besonders ausgeprägt war und somit auf eine veränderte Objektvervollständigung hindeutet. Die generelle Aktivierungsabnahme in rechts lateralisierten extrastriären und posterior parietalen Arealen korrelierte positiv mit der Intensität visueller Halluzinationen.

Möglicherweise ist die Aktivierung des 5-HT2A Rezeptors für die Effekte von Psilocybin auf die visuell-evozierten Potentiale während der modalen Objektvervollständigung verantwortlich und führt außerdem zu einer erhöhten Erregbarkeit des visuellen Kortex, was in der Bildung von Psilocybin-induzierten visuellen Halluzinationen unterliegen könnte. Um diese Hypothesen zu prüfen wurden in der dritten Studie (Kapitel 4) die Effekte von Psilocybin (215 µg/kg vs. Placebo) auf die alpha Oszillationen, welche die Erregbarkeit regulieren, sowie auf die früher visuell evozierten Potentiale (P1 und N170) bei 15 gesunden Probanden untersucht. Um den spezifischen Beitrag des 5-HT2A Rezeptors zu isolieren, wurde den Probanden zudem der präferentielle 5-HT2A Rezeptor Antagonist Ketanserin verabreicht (50 mg vs. Placebo). Die Befunde ergaben, dass Psilocybin wie bereits in Studie 2 selektiv die mediale P1 erhöht, Ketanserin das P1 Potential jedoch über den gleichen medialen Elektroden reduziert. Ferner wurde das darauffolgende N170 Potential durch Psilocybin reduziert, was mit dem Erscheinen von perzeptuellen Störungen einherging. Da sowohl die N170 Reduktion als auch die perzeptuellen Störungen durch Ketanserinvorbehandlung aufgehoben wurden, unterliegt diesen Veränderungen wahrscheinlich die Aktivierung des 5-HT2A Rezeptors. Schliesslich stellten wir fest, dass Psilocybin die Power der alpha Oszillationen vor dem Erscheinen visueller Reize reduzierte, hingegen die Stimulus induzierte Alpha Desynchronization blockierte – zwei Effekte, die wiederum durch Ketanserinvorbehandlung aufgehoben wurden. Dies legt nahe, dass die Aktivierung von 5-HT2A Rezeptoren einen visuellen Verarbeitungsmodus induziert, welcher dadurch gekennzeichnet ist, dass die Stimulusinduzierte Erregung von spontan strukturierter neuronaler Erregung überwältigt wird.

Zusammenfassend deuten diese Befunde darauf hin, dass Psilocybin die bewussten, die verhaltensbezogenen und die neurophysiologischen Prozesse der emotionalen und visuellen Verarbeitung hauptsächlich durch die Aktivierung von 5-HT2A Rezeptoren moduliert. Der identifizierte Effekt

der 5-HT2A Rezeptoraktivierung auf die emotionale Verarbeitungstendenzen stellt einerseits einen möglichen Mechanisms dar, welcher für die Pathophysiologie von dysfunktionalen emotionalen Verarbeitungstendenzen in der Depression wichtig sein könnte, und legt andererseits ein Rahmenprogramm nahe, um den mutmasslichen antidepressiven Effekt von Psilocybin und verwandten Substanzen in affektiven Störungen weiter zu elaborieren. Des Weiteren deckten die experimentellen Studien verschiedene 5-HT2A Rezeptor-abhängige neurophysiologische Mechanismen der veränderten visuellen Verarbeitung auf. Insbesondere wurde die Reduktion des N170 Potentials durch die 5-HT2A Rezeptoraktivierung als ein Schlüsselprozess in der Vermittlung von visuellen Halluzinationen und veränderter modalen Objektvervollständigung identifiziert, welche nicht nur in den Psilocybin-induzierten Zuständen, sondern auch in der Pathophysiologie der Schizophrenie und der Parkinson-Erkrankung eine zentrale Rolle spielen könnte.

1

General introduction

1.1 Significance of 5-HT2A and 1A receptors in emotional and visual processing

Increasing evidence point to a critical role for the 5-HT2A and 1A receptors in emotional and visual processing and suggest that these receptors are implicated in the pathogenesis of various psychiatric disorders, including schizophrenia, Parkinson's disease, mood and anxiety disorders.

The importance of the 5-HT2A and 1A receptors in emotional processing is indicated by the high expression levels of these receptors in an extended prefrontal-limbic network (Weisstaub et al., 2006; Albert and François, 2010; Richardson-Jones et al., 2010) that underlies emotional functions, including emotional control and recognition (Pessoa and Adolphs, 2010; Disner et al., 2011). Furthermore, alterations in 5-HT2A and 5-HT1A receptor densities were found in depressive (Yatham et al., 1999; Albert and François, 2010), bipolar (Sullivan et al., 2009; Yatham et al., 2010), and anxiety disorders (Perani et al., 2008; Akimova et al., 2009), which suggests that these receptors are also involved in the pathophysiology of mood and anxiety disorders. For instance, in patients with major depression, the prefrontal 5-HT2A receptor density is increased (Meyer et al., 1999; Meyer et al., 2001; Bhagwagar et al., 2006; Shelton et al., 2009), which is associated with pessimistic thinking (Meyer et al., 2003; Bhagwagar et al., 2006) and suicidal behaviour (Pandey et al., 2002; Oquendo et al., 2006; Shelton et al., 2009). Accordingly, the 5-HT2A and 5-HT1A receptors could be a key target in the treatment of emotional dysfunctions. This view is supported by the finding that chronic treatment with selective serotonin reuptake inhibitors (SSRIs) downregulates 5-HT2A receptors in the prefrontal cortex (PFC) in temporal association with the onset of clinical efficacy (Sibille et al., 1997; Gómez-Gil et al., 2004; Yamauchi et al., 2006). In addition, 5-HT1A receptors have been implicated in the antidepressive action of SSRIs by the findings that 5-HT1A-null mice are unresponsive to SSRI treatment (Santarelli et al., 2003) and that a selective reduction of 5-HT1A autoreceptor expression in the nucleus raphe permits a robust response to SSRI treatment in mice that do not otherwise respond (Richardson-Jones et al., 2010).

In contrast to the increasingly recognised significance of the 5-HT2A and 1A receptors in emotional processes, their roles in visual processing have only recently been acknowledged. Specifically, the 5-HT2A (Watakabe et al., 2009; Moreau et al., 2010) and 1A (Dyck and Cynader, 1993; Gerstl et al., 2008; Watakabe et al., 2009) receptors are highly expressed in the visual cortex, and alterations in their cortical density in Parkinson's disease (Ballanger et al., 2010; Huot et al., 2010) and schizophrenia (González-Maeso et al., 2008) are associated with the appearance of visual hallucinations. Moreover, the activation of the 5-HT2A receptor by indolamine hallucinogens such as psilocybin induces marked subjective visual distortion and hallucinations (Vollenweider et al., 1998), whereas the unselective 5-HT2A antagonist mianserin (Ikeguchi and Kuroda, 1995) and the 5-HT2A receptor inverse agonist pimavanserin (Meltzer et al., 2010) reduced the appearance of visual hallucinations in Parkinson's disease.

1.2 Using the indolamine psilocybin to elucidate the role of serotonergic subreceptors in emotional and visual processing

These recently accumulated evidence from molecular, pharmacological and neuroimaging studies converge on the view that the 5-HT2A and 1A receptors play critical roles in emotional and visual processing. Alterations in 5-HT2A and 1A receptors expressions are further implicated in the pathogenesis of emotional and visual dysfunctions in various psychiatric disorders, and therefore could be key targets in the treatment of visual and emotional dysfunction. However, human studies on the roles of the 5-HT1A, and in particular, the 5-HT2A receptors were mostly based on post-mortem samples or on PET using radioactive 5-HT2A ligands, such as altanserin, to reveal correlations between receptor density and self-reported emotional and visual states and traits. Thus, the effects of the activation of the 5-HT1A and especially the 5-HT2A receptors on emotional and visual processing functions in human subjects remain largely unknown. Furthermore, the neurophysiological mechanisms that mediated between 5-HT2A receptor activation on the one hand and emotional dysfunctions and the formation of visual hallucinations on the other hand were only addressed in a few animals studies, and therefore remain to be elucidated in further studies.

To elucidate these issues further, in the three experimental studies of this thesis (Chapters 2–4), the indolamine hallucinogen psilocybin, whose bioactive metabolite psilocin activates the 5-HT2A and 1A receptors (Blair et al., 2000; Nichols, 2004) and induce strong subjective visual and emotional alterations, was administered to healthy human subjects. The effects on emotional and visual processing and the underlying neurophysiological mechanisms were assessed by means of various self-report, behavioural and neurophysiological measurements. Furthermore, in two studies, the specific contribution of the 5-HT2A receptor stimulation to the psilocybin-induced effects was determined by pretreating subjects with the preferential 5-HT2A receptor antagonist ketanserin one hour before psilocybin administration. This pharmacological manipulation schema provides the unique prospect of experimentally manipulating the activity relative selectively at the 5-HT2A receptor and measuring its effects on psychological and neurophysiological processes in human subjects.

As I will briefly show in the next section, investigations into the effects of indolamine hallucinogens not only can contribute to unravelling the serotonergic mechanisms of psychological processes (Chapter 1.3.1) but also have a long history of being utilized in psychiatric research, either as a research tool to elucidate the psychogenesis of psychiatric disorders or as a therapeutic agent (Chapter 1.3.2). I will then show that this conceptual framework of the use of hallucino-

gens in psychiatric research can be applied to the investigation of emotional (Chapter 1.3.3) and visual processes (Chapter 1.3.4) and thereby may lead to unique insides into the pathophysiology and treatmet of psychiatric disorders, including mood disorders, schizophrenia and Parkinson's disease. I will infer several preliminary hypotheses based on the sparse knowledge of the effects of emotional and visual processing in animals and humans, whereas in Chapter (1.4 and 1.5), the hypothesis will be specified and the methodological approaches will be delineated.

1.3 Concepts and evidence in indolamine hallucinogen research

1.3.1 The contribution of indolamine hallucinogens to the understanding of the serotonergic system

In the middle of the 20th century the discovery of the similarities in chemical structure between indolamines and serotonin suggested that the serotonergic system might be responsible for the strong psychological effects of indolamine hallucinogens and further prompted the use of indolamine as a research tool to unravel the serotonergic mechanisms underlying psychological processes (Gaddum, 1953; Woolley and Shaw, 1954). Meanwhile, numerous studies have revealed that indolamine hallucinogens are agonists of various serotonin receptors, including the 5-HT2A, 5-HT1A, 5-HT2C, and 5-HT7 receptors (Nichols, 2004; Ray, 2010). However, the subjective effects of these hallucinogens are predominantly mediated by agonistic action at the 5-HT2A receptor (Vollenweider et al., 1998; Carter et al., 2005; Quednow et al., 2011), whereas the activation of both the 5-HT1A and 2A receptors appears to contribute to specific behavioural effects (Halberstadt and Geyer, 2011; Halberstadt et al., 2011). The activation of cortical 5-HT2A receptors by indolamine hallucinogens or serotonin induces an increase in glutamatergic recurrent network activity (Béïque et al., 2007; Moreau et al., 2010) associated with a robust increase in excitatory postsynaptic currents (EPSCs) predominantly within the layer 5 pyramidal neurons (Aghajanian and Marek, 1997, 1999; Béïque et al., 2007; González-Maeso et al., 2007; González-Maeso et al., 2008) that is thought to be critical in producing the consciousness-altering effects of the hallucinogen (Béïque et al., 2007; Aghajanian, 2009).

In addition to these local cortical effects of 5-HT2A receptor activation, hallucinogen research studies contributed to delineating the systemic effects of 5-HT2A receptor stimulation within a network comprising the prefrontal cortex, the nucleus raphe and the ventral tegmental area (Celada et al., 2001; Puig et al., 2003; Béïque et al., 2007; Vázquez-Borsetti et al., 2009). For instance, activation of 5-HT2A receptors in the mPFC increases the firing rate of serotonergic neurons in the dorsal raphe and of dopaminergic neurons in the ventral tegmental areal (VTA), resulting in an increased release of 5-HT in the mPFC (Celada et al., 2001; Puig et al., 2003; Vázquez-Borsetti et al., 2011) and of dopamine in the mesocortical areas (Vázquez-Borsetti et al., 2009; Vázquez-Borsetti et al., 2011).

Although these hallucinogen research studies made a strong contribution to the understanding of cellular and systemic serotonergic mechanisms, in particular of prefrontal cortex processing functions, only a small number of studies have used indolamine hallucinogens to delineate the serotonergic bases of emotional and visual function. However, from a psychiatric research view, these studies may provide unique insights into the psychopathology and treatment of psychiatric disorders.

1.3.2 The contribution of indolamine hallucinogens to the understanding of the psychophysiology and treatment of psychiatric disorders

The idea to use hallucinogens in psychiatric research derived in the early 1950s from the observation that indolamine profoundly alter conscious state, characterized by visual illusions and hallucinations, heightened mood and euphoria, altered sense of time, and loss of ego boundaries (Studerus et al., 2011). Researchers with different theoretical and experimental background have emphasized different aspects of this psilocybin-induced altered state, which resulted in diverse approaches to use hallucinogen in psychiatric research (Vollenweider and Kometer, 2010).

Several researchers emphasised that indolamine hallucinogens can enhance self-awareness and can increase the recall of repressed memories (Sandison, 1954; Schmiege, 1963). This unique property prompted the use of hallucinogens as an adjunct to facilitate the psychodynamic process during psychotherapy (Vollenweider and Kometer, 2010). Accordingly, the therapeutic use of indolamines was tested in the 1950s and 1960s in various psychiatric disorders, and numerous studies provided particularly promising results in mood and anxiety disorders (Sandison, 1954). This history converge with recent findings that 5-HT2A and 1A receptor are implicated in the pathophysiology and treatment of mood disorders (Chapter 1.1.) and that indolamines alters the functioning of the 5-HT2A and 1A receptor (Chapter 1.3.3). Together these findings indicate that an understanding of the emotional effects of psilocybin provides insights into the mechanisms underlying mood disorders and the putative antidepressant effect of psilocybin.

Other researchers from the early 1950s emphasised that indolamines induce perceptual distortions, thought disorder and depersonalisation and derealisation experiences (Hoch et al., 1952; Leuner, 1962). Because these symptoms similarly occur in psychotic disorders, this perspective has prompted the use of serotonergic hallucinogens as research tools to mimic psychotic states and investigate them under controlled experimental conditions (Geyer and Vollenweider, 2008), a research approach that is known as model psychosis. Meanwhile, this approach have been corroborated by studies showing that 5-HT2A receptor densities in the PFC is altered in drug-naive schizophrenic patients (Hurlemann et al., 2008; González-Maeso et al., 2008) and that antagonism at 5-HT2A receptor is implicated in the effects of atypical antipsychotics such as clozapine, risperidone or olanzapine (Lieberman et al., 1998; Meltzer, 1999) (Olajossy-Hilkesberger et al., 2011). However, it must be clearly emphasized that no transient state produced by any drug can mimic the entire spectrum of symptoms and dysfunctions of a complex group of disorders such as schizophrenia spectrum disorders. In this respect it has been shown that psilocybin mimics in particular positive symptoms of psychosis, including visual hallucinations (Gouzoulis-Mayfrank et al., 1998; Geyer and Vollenweider, 2008), which is in line with the finding that 5-HT2A receptor density is associated with the formation of visual hallucinations in schizophrenia (González-Maeso et al., 2008). Interestingly, increase density of 5-HT2A

receptor in visual pathways was recently found in Parkinson's patients with hallucinations (Ballanger et al., 2010; Huot et al., 2010), which indicates that investigations into the visual effects of psilocybin might not only provide insights into the serotonergic mechanism underlying the formation of visual hallucinations in schizophrenia, but also in Parkinson's disease.

1.3.3 The effects of indolamine hallucinogens on emotional processing

The mood-enhancing effects of indolamines were early on recognised in unsystematic phenomenological studies (DeShon et al., 1952), and the promising therapeutic effect of indolamine hallucinogens in anxiety and depression (Leuner, 1962; Pahnke et al., 1969) suggests that indolamines also induce sustainable changes in emotional processing. Although these studies from the 1950s and 1960s had serious methodological flaws by contemporary standards and remained mostly unreplicated after 1970 because of political restrictions, converging lines of recent evidence from animal and human studies support the putative therapeutic potential of indolamines in mood and anxiety disorders (Vollenweider and Kometer, 2010). This view is indicated by the finding that indolamine hallucinogens induce several neuroplastic adaptations in an extended prefrontal-limbic network that are similarly induced by SSRI treatment in depressive subjects and are associated with the therapeutic efficacy of SSRIs (Vollenweider and Kometer, 2010). For instance, the indolamine hallucinogen LSD downregulates cortical 5-HT2A but not 5-HT1A receptor expression, most prominently in the PFC (Buckholtz et al., 1990; Gresch et al., 2005). This indolamine-induced 5-HT2A receptor downregulation might be associated with an antidepressive effect, as 5-HT2A receptor density was found to be increased in the PFC in patients with depression (Meyer et al., 1999; Meyer et al., 2001; Bhagwagar et al., 2006; Shelton et al., 2009) and was found to be reduced after chronic treatment with SSRIs at the onset of clinical efficacy (Sibille et al., 1997; Gómez-Gil et al., 2004; Yamauchi et al., 2006). Support for an antidepressive and anxiolytic effect of the indolamine hallucinogen DOI was revealed in various animal models, including the elevated plus maze (Nic Dhonnchadha et al., 2003; Massé et al., 2007; Nunes-de-Souza et al., 2008; Gomes and Nunes-De-Souza, 2009), the elevated T maze (da Silva et al., 2011), the four-plate test (Massé et al., 2007) and tonic immobility (Donatti and Leite-Panissi, 2009). Furthermore, animal studies revealed that 5-HT2A receptor stimulation has an inhibitory effect on subcortical structures, such as the amygdala (Donatti and Leite-Panissi, 2009; Jiang et al., 2009; Hale et al., 2010; Bombardi, 2011), and the periaqueductal grey (PAG) (Castilho et al., 2002; Millan et al., 2002; Gomes and Nunes-De-Souza, 2009), which might be beneficial for the treatment of mood and anxiety disorders. Most recently, the antidepressive and anxiolytic potential is supported by the first recent placebo-controlled pilot study in human terminal cancer patients, which demonstrated that a single dose of psilocybin led to a gradual reduction in depressive symptoms and trait anxiety over a period of six months (Grob et al., 2011).

Taken together, these findings on the emotional effects of indolamines are not only in line with a key role of 5-HT2A and 1A receptors in emotional processing (Chapter 1.1) but also indicate that indolamines can be used to further the understanding of the serotonergic mechanisms underlying affective disorders and can possibly be even used as agents in the treatment of affective disorders.

To approach these issues further, we assessed the effects of psilocybin and ketanserin on various emotional processing biases, which are defined as the preferential processing of positive or negative information (Disner et al., 2011; Elliott et al., 2011). Assessing emotional processing biases might, on the one hand, be particularly informative because emotional processing biases have been strongly implicated in the pathophysiology of affective disorders (Disner et al., 2011). In depressed subjects emotional processing is often biased towards negative versus positive information across psychological domains, such as perception, attention, memory and decision-making (Mathews and MacLeod, 2005; Disner et al., 2011; Roiser et al., 2012). For instance, depressed subjects need more intensely happy facial expressions to correctly label happiness (Joormann and Gotlib, 2006) and are slower in responding to positive but not to negative words in emotional go/nogo tasks (Murphy et al., 1999; Erickson et al., 2005). On the other hand, a crucial role for serotonin (5-HT) in the regulation of emotional biases is evidenced by genetic and pharmacological studies, whereas the differential contributions of 5-HT subreceptors across psychological emotional domains in humans are less well-understood (Elliott et al., 2011; Sharp and Cowen, 2011). Therefore, investigations into the effect of psilocybin and ketanserin on emotional processing biases across psychological domains can help to clarify the role of serotonin in emotional processing biases.

1.3.4 The effects of indolamine hallucinogens on visual processing

Surprisingly, the effects of indolamine hallucinogens and 5-HT2A stimulation on visual processing remain largely unknown, although the term “hallucinogen” suggests that understanding visual hallucinations would be a central research focus. Only sparse knowledge derives from early phenomenological studies indicating that low doses of indolamines induce a subjective increase in the brightness of surrounding objects and colours, whereas at medium doses, objects additionally appear to drift and pulsate (Siegel and Jarvik, 1975). In addition to these perceptual illusions, elementary visual hallucinations of light flashes and simple geometrical patterns occur. Specifically, low-level features of the visual environment are grouped into elementary geometrical patterns, which can be classified into four categories called form constants: (I) tunnels and funnels; (II) spirals; (III) latencies, including honeycombs and triangles; and (IV) cobwebs (Klüver, 1966). Perceptions of animals, humans or scenes, however, are mostly restricted to the closed-eyes condition (Siegel and Jarvik, 1975), indicating that serotonergic hallucinogens more

typically induce elementary rather than complex hallucinations. More recently, computational models suggested that these elementary visual hallucinations can be caused by an increase in the excitability of the visual neuronal network that leads to a destabilisation of spontaneous visual network activity (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012). The activation of 5-HT2A receptors by the indolamine hallucinogen DOI was found to increase the excitability of the visual cortex in rats (Moreau et al., 2010), which support the notion that indolamine induce elementary hallucinations by increasing excitability.

The first recent human studies revealed that the psilocybin-induced self-reported perceptual alterations, ranging from illusions to elementary and complex hallucinations, can be antagonized by ketanserin, which indicates that 5-HT2A receptor activation mediates these visual phenomena (Vollenweider et al., 1998; Carter et al., 2004; Quednow et al., 2011). Furthermore, a human neuroimaging study using PET found that psilocybin increased activity in the occipital cortex most prominently in lateral rather than medial areas during resting state (Vollenweider et al., 1997). Psilocybin also disrupted in behavioural task global motion detection, which is thought to be mediated by the extrastriate area MT, but not local motion detection, which is resolved in V1 (Carter et al., 2004). Together, these findings suggest that psilocybin might exert a stronger influence on extrastriatal, rather than striatal functions.

Taken together, the preliminary findings from indolamine research studies indicate that 5-HT2A receptor activation by psilocybin might, on the one hand, promote the formation of elementary visual hallucinations by increasing the excitability of the visual cortex and, on the other hand, disrupt extrastriate processing. To elucidate these issues further, we tested whether psilocybin modulates alpha oscillations, which have been identified as the most crucial mechanism in the regulation of excitability in human subjects (Thut et al., 2006; Romei et al., 2008a; Jensen and Mazaheri, 2010; Klimesch, 2011; Mathewson et al., 2011), and thereby promotes visual hallucinations. Furthermore, we assessed the effect of psilocybin on modal object completion because this fundamental visual process relies heavily on extrastriate visual areas (Hirsch et al., 1995; Ffytche and Zeki, 1996; Mendola et al., 1999; Seghier and Vuilleumier, 2006; Knebel and Murray, 2012) and has been shown to be disrupted in schizophrenia (Spencer et al., 2003; Spencer et al., 2004; Foxe et al., 2005).

1.4 Approaching the assessment of the emotional effects of psilocybin and ketanserin

1.4.1 Overview of the goal and methodological approaches of the emotional experiments

In the previous chapters I have shown that a crucial goal of this thesis is to gain insights into the effect of psilocybin on emotional processing and to elucidate the contribution of the 5-HT2A receptor to emotional processing. These insights might help us to identify possible mechanism implicated in the pathophysiology and treatment of mood disorders and the putative antidepressive effect of psilocybin.

To this end, the effect of psilocybin on the emotional processing bias in emotional face recognition, goal-directed behaviour and mood states was assessed in 17 healthy human subjects using self-report, behavioural and neurophysiological measurements. The specific contribution of the 5-HT2A receptors was disentangled by additionally administering the preferential 5-HT2A antagonist ketanserin one hour before the administration of psilocybin (see Chapter 2 for details). In the following paragraphs, I will explain why assessing the emotional bias in facial recognition, goal-directed behaviour and mood states is particularly informative and how these three psychological domains were operationalised.

1.4.2 Emotional face recognition

The ability to accurately recognise the emotional state of a person by looking at their facial expression is fundamental for social interaction. In patients with major depression, emotional face recognition is biased towards the recognition of negative versus positive emotions (Gur et al., 1992; Joormann and Gotlib, 2006; Victor et al., 2010; Elliott et al., 2011), which contributes to interpersonal difficulties (Gur et al., 1992) and influences the relapse rate during remission episodes (Bouhuys et al., 1999).

A key role of the serotonergic system in the pathogenesis of this negative bias in facial recognition is, on the one hand, evidenced by genetic studies showing increased attention (Beevers et al., 2009) and amygdala response (Hariri et al., 2002; Furmark et al., 2004; Canli et al., 2005; Hariri et al., 2005; Heinz et al., 2005) to negative faces in short-allele carriers of the 5-HTTLPR polymorphism. On the other hand, various forms of serotonergic manipulations, including SSRI (Harmer et al., 2003b; Bhagwagar et al., 2004; Browning et al., 2007; Victor et al., 2010), acute tryptophan depletion (ATD) (Murphy et al., 2002; Attenburrow et al., 2003; Harmer et al., 2003a; Marsh et al., 2006), MDMA (Bedi et al., 2010) and mirtazapine administration (Arnone et al., 2009; Rawlings et al., 2010), have been shown to modulate the emotional face recognition bias. Interestingly, a single dose of SSRIs increased the recognition of negative emotions in

most studies (Harmer et al., 2003b; Browning et al., 2007), whereas chronic SSRI administration decreased the recognition rate (Harmer et al., 2004). Furthermore, only chronic SSRI administration decreased the 5-HT2A receptor density (Sibille et al., 1997; Meyer et al., 2001; Yamauchi et al., 2006), which suggested that changing activity at the 5-HT2A receptors might shift the emotional processing bias in facial recognition.

To investigate this hypothesis further, we assessed the effect of psilocybin and the preferential 5-HT2A receptor antagonist ketanserin on the recognition of subtle emotional states from the eye regions of the faces of others. We investigated whether subjects exhibited a bias toward the recognition of positive, negative or neutral emotional states. In doing so, we used a German version of the "Reading the Mind in the Eyes Test" (Baron-Cohen et al., 2001), but adapted the scoring of the test (see Chapter 2 for details) to assess the total number of correct recognitions separately for the eye regions of faces depicting positive, negative and neutral mental states.

1.4.3 Emotional goal-directed behaviour

Emotional goal-directed behaviour in social environments requires the selection and inhibition of appropriate responses to emotional cues. This process has been operationalised by the emotional go/nogo task, in which subjects must respond to emotional cues with a certain valence (e. g., negative) and inhibit response to cues with a different valence (Murphy et al., 1999). The performance of this task relies on an prefrontal-limbic network, which comprises the anterior cingulated cortex (ACC), the right inferior prefrontal cortex, the amygdala, the orbitofrontal cortex and the insula (Elliott et al., 2000, 2002; Hare et al., 2005; Goldstein et al., 2007; Chiu et al., 2008; Schulz et al., 2009; Albert et al., 2011), and regulates the interaction between emotion and cognition and the response control processes (Schulz et al., 2009; Disner et al., 2011; Elliott et al., 2011). The convergence of these processes may occur during the time range of the N2 and P300 event-related potentials, as both potentials are influenced by both the emotional content and the inhibitory control over the responses to these cues (Chiu et al., 2008; Krompinger and Simons, 2009; Albert et al., 2010; Zhang and Lu, 2012).

Importantly, performance and neuronal activity in the emotional go/nogo task vary depending on the pathological state on the continuum between depression and mania (Murphy et al., 1999; Erickson et al., 2005; Kyte et al., 2005; Kaplan et al., 2006; Wessa et al., 2007; Gopin et al., 2011). Specifically, in subjects with major depression, the reaction times and/or error rates are biased toward negative emotions (Murphy et al., 1999; Erickson et al., 2005; Kyte et al., 2005; Kaplan et al., 2006; Wessa et al., 2007), whereas the response pattern in acute mania is strongly biased toward positive emotions (Murphy et al., 1999). In depressed subjects, increased activity in the

ventral ACC (Elliott et al., 2002) and an increased P300 component (Krompinger and Simons, 2009) in response to negative stimuli might underlie the negative emotional processing bias in the go/nogo task.

Alterations in the serotonergic tone have been implicated in the pathogenesis of this negative bias by several studies showing that the positive response bias, which is usually observed in healthy subjects (Murphy et al., 2002; Erickson et al., 2005; Roiser et al., 2008; Robinson and Sahakian, 2009; Feder et al., 2011), is abolished by ATD (Murphy et al., 2002; Roiser et al., 2008; Robinson and Sahakian, 2009), most prominently in healthy subjects having first-degree relatives with recurrent or chronic major depression (Feder et al., 2011).

To assess the influence of psilocybin and 5-HT2A receptor activation on the emotional bias in goal-directed behaviour, we used an emotional go/nogo task with positive, negative and neutral words as the cues (Murphy et al., 1999; Elliott et al., 2000; Chiu et al., 2008; Elliott et al., 2011). Words were used as stimulus material to be able to better differentiate the performance in this task from the emotional face-recognition task. That is, words have a stronger impact on cognitive processes, whereas faces more strongly influence perception (Frühholz et al., 2011). In this respect, the use of words also reduces the possible confounding influence of the strong visual effects of psilocybin on emotional processing. Specifically, the valences of faces have been suggested to be partially coded by visual features (Calvo and Nummenmaa, 2008) and configurations (Narme et al., 2011), whereas these visual properties do not usually constitute the difference between words with different valences. Therefore, a psilocybin-induced disruption in the processing of visual features and configurations is unlikely to alter the differentiation of the valences of words but might influence the differentiation of the valences of faces. To further reduce confounding variables, the number of letters, syllables, phonemes, frequency of appearance, number of orthographic neighbours and imaginability were matched between different word valences. Finally, the typical emotional go/nogo task was extended by parametrically manipulating the number of go cues preceding the nogo cues in the trial order from 0–6 in each valence condition. This experimental configuration allows the assessment of sequential emotional facilitatory and inhibitory processes, such as a decrease in RTs with repeated negative stimuli, that have been implicated in the pathophysiology of mood disorders (Joormann, 2004; Goeleven et al., 2006; Markus and De Raedt, 2011). Taken together, the emotional valence (pos/neu/neg), the task instruction (go/nogo) and the sequential context (0–6) were manipulated, and the effects of these experimental factors on behavioural (RT and error rates) and electrophysiological (N2 and P300 amplitude) parameters were assessed in psilocybin and ketanserin induced-states.

1.4.4 Mood

Alterations in the mood state are a defining psychopathological characteristic of depression and mania. Although the mood state is usually not acutely altered by substances that modulate the serotonergic tone, such as SSRIs (Harmer et al., 2003b; Bhagwagar et al., 2004; Harmer et al., 2008) and ATD (Hayward et al., 2005; Robinson and Sahakian, 2009; Roiser et al., 2009), indolamines are known for their acute mood-altering effects (Studerus et al., 2010). Therefore, 5-HT2A receptors activation might be more closely linked to the acute mood state than is the serotonergic tone. To further characterise the mood-altering effects of psilocybin and 5-HT2A agonism, we used the clinically relevant rating scale Positive and Negative Affect Schedule (PANAS) to assess the self-reported positive and negative affect (Watson et al., 1988; Krohne, 1996) and the State-Trait Anxiety Inventory (STAI) to quantify state-anxiety (Spielberger et al., 1983).

1.5 Approaching the assessment of the visual effects of psilocybin and ketanserin

1.5.1 Overview of the goal and methodological approaches of the visual experiments

In the previous chapters I have shown that crucial goals of this thesis are to: elucidate the effects of psilocybin on visual processing; disentangle the specific contribution of the 5-HT2A receptor to these psilocybin-induced effects; and thereby gain insights into the pathophysiological mechanism underlying visual hallucinations in schizophrenia and Parkinson's disease.

To this end, the idea that psilocybin might particularly impair extrastriate visual processing functions was addressed in the first visual study by assessing the effects of two different doses of psilocybin (125 µg/kg and 250 µg/kg vs. placebo) on the spatiotemporal dynamic of modal object completion in 17 subjects using visual-evoked potential recordings in conjunction with topographic mapping and source analysis. These effects were then related to the intensity of the self-reported psilocybin-induced visual hallucinations, and compared to the previously observed deficits in schizophrenia (see Chapter 3 for details).

To disentangle the specific contribution of the 5-HT2A receptor to the psilocybin-induced effects on visual-evoked potentials in the modal object completion task, we conducted a second study in which we pretreated 15 healthy human subjects with the preferential 5-HT2A antagonist ketanserin (50 mg) one hour before they received psilocybin (215 µg/kg) (see Chapter 4 for details).

The data from the second visual study were additionally used to address the idea that psilocybin might modulate alpha oscillations by 5-HT2A receptor activation, which would lead to a change in the visual network excitability that might underlie the formation of visual hallucinations. Therefore, we computed the prestimulus and subsequent visual stimulus-induced parieto-occipital alpha oscillations using single-trial wavelet analysis. These effects were again related to the self-reported psilocybin-induced subjective visual effects (see Chapter 4 for details).

In the following section, I will briefly discuss recent findings on modal object completion, as well as on alpha power and phase to infer several hypotheses regarding the effect of psilocybin and ketanserin.

1.5.2 Modal object completion

Modal object completion refers to the illusory perception of object boundaries and their enclosing surfaces in the absence of any direct sensory information depicting these boundaries or surfaces. The ability to interpolate the existence of object surface boundaries is essential for accurate object recognition in situations in which only ambiguous or incomplete retinal information of the object is available due to partial occlusion or poor illumination.

Which brain areas are responsible for achieving modal completion remains debated, with the involvement of the primary visual cortex (V1) being particularly contentious (Seghier and Vuilleumier, 2006; Knebel and Murray, 2012). However, a variety of imaging studies provide strong evidence that the lateral occipital complex (LOC) and the early visual area V2 are likely to play major roles in this process (Hirsch et al., 1995; Ffytche and Zeki, 1996; Mendola et al., 1999; Seghier and Vuilleumier, 2006; Knebel and Murray, 2012). Electrophysiological studies additionally indicate that modal completion of simple figures, such as Kanizsa figures, is indexed by the modulation of the N170 component (Herrmann and Bosch, 2001; Pegna et al., 2002; Proverbio and Zani, 2002; Murray et al., 2004; Spencer et al., 2004; Foxe et al., 2005; Murray et al., 2006; Yoshino et al., 2006; Knebel and Murray, 2012), which appears to be driven primarily by the two critical processes underlying modal object completion: boundary completion (Murray et al., 2006) and region-based segmentation (Yoshino et al., 2006).

Abnormalities in the spatiotemporal brain dynamics of modal object completion have been reported in different psychiatric disorders, such as schizophrenia (Spencer et al., 2003; Spencer et al., 2004; Foxe et al., 2005), autism (Stroganova et al., 2007) and Williams syndrome (Grice et al., 2003). In schizophrenia, disturbances in modal object completion were characterised by decrements of the P1 (Spencer et al., 2003; Foxe et al., 2005) and a trend toward reduction (Spencer et al., 2003) or significant reduction of the N170 component (Spencer et al., 2004).

Direct evidence for the involvement of 5-HT2A or 1A receptors in the modulation of visual-evoked potentials in general, and modal object completion in particular, is lacking. However, psilocybin might modulate modal object completion, as this task relies on extrastriatal visual areas (Hirsch et al., 1995; Ffytche and Zeki, 1996; Mendola et al., 1999; Seghier and Vuilleumier, 2006; Knebel and Murray, 2012), which appear to be more strongly modulated by psilocybin than the striatal areas (see chapter 1.3.4). Understanding the influence of psilocybin and the contribution of 5-HT2A receptor activation on modal object completion is particularly compelling, not only because modal object completion is so critical in defining individual perceptual experience but also to elucidate possible serotonergic mechanisms implicated in the previously revealed disruptions in modal object completion observed in schizophrenia (Spencer et al., 2003; Spencer et al., 2004; Foxe et al., 2005).

To elucidate these issues further, we used the data from both visual studies (see above). The data from the first visual study served to assess the spatiotemporal dynamics of modal object completion. This assessment included the analysis of: (I) the scalp topography, (II) the source localisation and (III) the visual-evoked potential waveforms. This combination of analysis methods has been increasingly used in recent years, as it reduces the experimenter bias associated with the selection of an appropriate time window for the statistical analysis of the components (Murray et al., 2008). In brief, during the topographic analysis, the predominant topographies (also called the template map) appearing in the normalised, group-averaged ERPs as a function of time, and experimental condition were identified by means of a spatial k-means cluster

analysis (Pascual-Marqui et al., 1994; Brandeis et al., 1995). In a second step, it was statistically verified that the maps identified at the group-averaged level also appeared on the individual subject level. The extracted time frames of the template maps were subsequently used to calculate the mean amplitude of the P1, N170 and P300 components of the visual-evoked potential. Finally, standardised low-resolution electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) was used to estimate the three-dimensional intra-cerebral current density distributions underlying the ERPs within the time frames defined by the topographic analysis.

1.5.3 Alpha Power and Phase

Alpha oscillations (8–12 Hz) have been identified as a major neural mechanism that regulates by inhibition the excitability level of cortical sensory networks (Foxe et al., 1998; Thut et al., 2006; Klimesch et al., 2007; Rihs et al., 2007; Romei et al., 2008a; Romei et al., 2008b; Klimesch, 2011; Mathewson et al., 2011). This view is supported by the findings that low alpha power is associated with an increased firing rate of cortical neurons (Haegens et al., 2011) and with an increased likelihood to perceive TMS-induced phosphenes (Romei et al., 2008a; Romei et al., 2008b). Furthermore, alpha power decreases in anticipation of (Ergenoglu et al., 2004; Rohenkohl and Nobre, 2011; Stokes et al., 2012) or in response to a visual stimulus (Pfurtscheller et al., 1979; Klimesch, 2011), a change that is thought to reflect an adaptation of the excitability level of the visual cortical network for the optimal processing of the actual or forthcoming visual input. In line with this view, a low prestimulus alpha power is associated on a single-trial basis with an increased detection rate of the subsequent visual stimuli (Ergenoglu et al., 2004; Thut et al., 2006; Hanslmayr et al., 2007; van Dijk et al., 2008; Busch et al., 2009) and with higher visual-evoked potentials to the visual stimuli (Ergenoglu et al., 2004; van Dijk et al., 2008). Hence, alpha oscillations are increasingly recognised as a key mechanism in the regulation of visual perception. Nevertheless, the pharmacological base underlying this crucial role remains largely unknown.

A possible role of 5-HT2A receptor activation in the modulation of alpha power is indicated by the finding that 5-HT2A receptor activation increases the excitability of rat visual cortical networks (Moreau et al., 2010). This 5-HT2A receptor-mediated increase in the excitability might be caused by a decrease of alpha power. An increase in the excitability in the absence of direct sensory input destabilises the spontaneous network activity, which, according to computational models, results in the formation of elementary visual hallucinations (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012). Although this idea has not yet been directly tested in humans or animals, several findings are in line with this notion. For instance, the geometrical patterns that are produced by these computational models (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012) are phenomenologically similar to the geometrical elementary visual hallucinations that are produced

by indolamine hallucinogens (Klüver, 1966; Siegel and Jarvik, 1975). Furthermore, presenting these simple geometrical patterns to anesthetised cats induces patterned neuronal states that correspond to the self-organised, spontaneous patterned neuronal states (Kenet et al., 2003). Therefore, it has been postulated that a currently undefined inhibitory mechanism is necessary to prevent that the usually subliminal spontaneous neuronal activity leads to conscious precepts (Billock and Tsou, 2007; Butler et al., 2012). It is conceivable that alpha oscillations mediate this inhibition, as alpha oscillations are the key inhibitory mechanism in the visual network.

Taken together, these findings indicate that psilocybin might decrease alpha power by 5-HT2A receptor activation. This decrease of alpha power in the absence of visual stimuli (i.e., before stimulus presentation) would cause an increased excitability and therefore might lead to an increase in spontaneously generated neuronal activity that promotes the formation of visual hallucinations.

To confirm these hypotheses, we used the data from the second visual study (see above) and computed the alpha power and phase for the time range before and after the presentation of visual stimuli using a single-trial wavelet analysis (see chapter 4 for details). Briefly, the signal of each trial and at each time-point in the trial was convoluted with a family of Morlet wavelets. Subsequently, the power in each trial was computed as the sum of the squares of the real and imaginary Morlet wavelet components. Furthermore, using the phase information from the wavelet analysis, the amount of normalised phase variability across trials was quantified by the phase-locking value, PLV (also known as the intertribal coherence (ITC) or phase-locking factor). Subsequently, these measures were related to the self-reported intensity of the visual hallucinations quantified by the 5D-ASC questionnaire.

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2

Psilocybin biases facial recognition, goal-directed behavior, and mood state towards positive relative to negative emotions through different serotonergic subreceptors

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Personal contribution

M. K. conceived and designed the study, developed the emotional go/nogo task, gathered and analyzed all behavioral and EEG data, interpreted the data and wrote the paper. F. X. V., A. S., R. B., S. E. and S. E. helped to design the study, gather the data, interpret the data and/or revise the first draft of the paper.

2.1 Abstract

Background

Serotonin 1A and 2A receptors have been associated with dysfunctional emotional processing biases in mood disorders. These receptors further predominantly mediate the subjective and behavioral effects of psilocybin and might be important for its recently suggested antidepressive effects. However, the effect of psilocybin on emotional processing biases and the specific contribution of serotonin 2A receptors across different emotional domains is unknown.

Methods

In a randomized double-blind study 17 healthy human subjects received on four separate days placebo, psilocybin (215 µg/kg), the preferential 5-HT2A antagonist ketanserin (50 mg), or psilocybin plus ketanserin. Mood states were assessed by self-report ratings, and behavioral and event-related potential measurements were used to quantify facial emotional recognition and goal-directed behavior towards emotional cues.

Results

Psilocybin enhanced positive mood and attenuated recognition of negative facial expression. Furthermore, psilocybin increased goal-directed behavior towards positive compared to negative cues, facilitated positive but inhibited negative sequential emotional effects and valence-dependently attenuated the P300 component. Ketanserin alone had no effects but blocked the psilocybin-induced mood enhancement and decreased recognition of negative facial expression.

Conclusion

This study shows that psilocybin shifts the emotional bias across various psychological domains and that activation of 5-HT2A receptors is central in mood regulation and emotional face recognition in healthy subjects. These findings may not only have implications for the pathophysiology of dysfunctional emotional biases, but may also provide a framework to delineate the mechanisms underlying psylocybin's putative antidepressant effects.

2.2 Introduction

Central components in the pathophysiology of mood disorders are biases towards the processing of negative compared to positive emotions across different psychological domains including perception, attention and behavior. For example, depressed subjects need more intensely happy facial expression to correctly label happiness (1) and are slower in responding to positive but not

to negative words in emotional go/nogo tasks (2, 3). A crucial role for serotonin (5-HT) in the regulation of emotional biases is evidenced by genetic and pharmacological studies, while the differential contribution of 5-HT subreceptors across psychological domains in humans is less well-understood (4, 5). However, accumulating evidence suggests that 5-HT1A and 2A receptors are particularly implicated in the pathophysiology of dysfunctional emotional biases, because 5-HT1A and 5-HT2A receptor densities are altered in depressive (6–10), bipolar (11, 12), and anxiety disorder (13, 14). In line with this view, 5-HT1A receptor agonists such as buspirone or pindolol have been particularly used as add-on treatment to enhance the antidepressant effect of SSRIs (7). More recently, also preferential 5-HT2A receptor agonists revealed anxiolytic and antidepressive effects in different animal models of mood disorders (15–21). In humans activation of 5-HT2A receptors has been identified as the primary mechanism underlying the acute subjective effects of classical psychedelics such as psilocybin (22), which, at low to medium doses, are predominantly characterized by heightened mood and visual disturbances (23–25). Furthermore, psilocybin induces neuronal activity and neuroplastic effects in prefrontal-limbic circuits implicated in mood disorder (24). These findings suggest that psilocybin, whose bioactive metabolite psilocin activates 5-HT2A, 1A and 2C receptors (26, 27), may not only produce acute mood enhanging effects but may also induce sustained antidepressant or anxiolytic effects (24). In support of this view, a gradual reduction of depressive symptoms and trait anxiety over six month was observed after a single dose of psilocybin in a recent placebo-controlled pilot study in terminal cancer patients (28).

Taken together, these findings suggest that psilocybin might bias emotional processing away from negative information by activating 5-HT1A, 5-HT2A receptors or both receptors. Assessing this hypothesis might help to unravel the psychopharmacological mechanism underlying the pathophysiology of dysfunctional emotional biases and the recently proposed antidepressant and anxiolytic potential of psilocybin.

To this end, here we investigated for the first time the effect of psilocybin on emotional processing biases across psychological domains. We also disentangled the specific contribution of the 5-HT2A receptor by antagonizing it with ketanserin. First, we assessed behaviorally the ability to recognize the emotional state of another person from facial cues, which has been previously shown to be biased towards negative emotions in depressed and anxious subjects (1, 29–31) and to be related to serotonergic tone (29–33). Second, response selection and inhibition to emotional cues were quantified by behavioral and event-related EEG measurements in an emotional go/nogo task (2). These are crucial components of goal-directed behavior in social environments (34) and are regulated by the 5-HT system (35–37). Finally, we evaluated and quantified acute psilocybin-induced mood effects using clinical relevant rating scales.

2.3 Methods and Materials

2.3.1 Subjects

Seventeen healthy right-handed subjects (11 males, 6 females, mean age 26.0 ± 4.36 years, 15 university students/graduates, 1 highschool diploma, 1 apprenticeship) were recruited through advertisement from the University of Zurich. All subjects were healthy according to physical examination, including electrocardiography and detailed blood analysis. The Mini-International Neuropsychiatric Interview MINI-SCID (38), the DIA-X diagnostic expert system (39), and the Hopkins Symptom Checklist SCL-90-R (40) were used to exclude subjects with present or antecedent psychiatric disorders or a history of major psychiatric disorders in first-degree relatives. The absence of drug dependence or present drug abuse was verified by urine drug-screening and a self-report drug use questionnaire. Seven subjects reported having previous experiences with psilocybin or other hallucinogens (mean lifetime experiences 2.4 ± 1.1 times) and three subjects with MDMA (mean lifetime experiences 3.3 ± 2.5 times). Eight subjects reported to have rarley or sporadically used cannabis (< 4 joints / month).

Subjects were informed by a written and oral description about the procedures of the study, including that they will receive on each experimental day in a double-blind manner two substances, either placebo + placebo, placebo + psilocybin, ketanserin + placebo or ketanserin + psilocybin. Furthermore, they were informed about the possible risk of psilocybin administration and the broad spectrum of its consciousness altering effects that may range from alterations in sensory perception, mood, thought and the experience of self. To minimize the influence of the individual's expectations we emphasized that the psychological effect of psilocybin is known to vary largely between and within subjects. The study was approved by the ethics committee of the Canton of Zurich. The use of psilocybin in humans was authorized by the Swiss Federal Office of Public Health, Department of Pharmacology and Narcotics, Bern, Switzerland.

2.3.2 Experimental design

Using a double-blind within-subject placebo-controlled randomized design subjects received on 4 experimental days, separated from each other by at least 2 weeks, placebo or ketanserin (50 mg) (pretreatment) followed after 1 h by placebo or psyilocybin (215 µg/kg) (treatment). These specific doses were chosen, because they have previously been shown to effectively induce or block the associated changes in conscious states, respectively (41). The time delay between pretreatment and treatment was 1 h to ensure maximal 5-HT2A receptor occupancy. Experiments started approximately 130 min after treatment and self-report questionnaires were given 360 min posttreatment to retrospectively rate their subjective experience since drug intake.

2.3.3 Acute subjective drug effects

The Five Dimensions of Altered States of Consciousness (5D-ASC) questionnaire (42), a self-rating scale with 94 visual analogue items, was used to quantify the subjective psychological effects of psilocybin. Eleven subscales were recently constructed (43). Of primary interest in regard to the current study was the "Blissful State" subscale measuring experiences of pleasure, peace and love and the "Anxiety" subscale quantifying anxiety associated with derealisation and depersonalization. The German version of the Positive and Negative Affect Schedule (PANAS) was used to assess the self-reported positive and negative affect (44, 45) and the German version of State-Trait Anxiety Inventory (STAI) was used to quantify state-anxiety (46).

2.3.4 Facial emotional recognition

The accuracy of inferring emotional states from the eye region was measured by a German adaptation of the "Reading the Mind in the Eyes Test" (47). Briefly, 36 black-and-white photographs of the eye region of persons expressing different subtle emotional states (eg. ashamed) were presented on a computer screen together with four words describing the states of the persons. Participants were instructed to choose the word which described the state of the person most accurately. The total number of correct recognitions was computed for different valence categories (positive, negative and neutral). Because the previously used valence categorization (48) was based on a small sample of 12 undergraduate women who rated the picture in combination with the target word, pictures and target/distracter words were rerated seperately in a study comprising 40 subjects (Supplementary information).

2.3.5 Emotional go/nogo task

In the emotional go/nogo task, emotionally valenced words (positive, negative, neutral) were presented in easy readable font ("Universe") in the middle of the computer screen. We used emotional words as stimulus material because they have, in contrast to faces, a stronger impact on cognitive versus perceptual processes (49) and therefore allow better differentiation of the performance in the emotional go/nogo from the facial recognition task. Participants were instructed by text appearing at the beginning of each block to press as rapidly as possible a response bottom when words of one valence category are presented ("go" cues) and withhold responses to words of another valence category ("nogo" cues). The following blocks were presented once in the first and once in the second half of the experiment in a randomized order: (1) positive go, neutral nogo, (2) positive go, negative nogo, (3) neutral go, positive nogo, (4) neutral go, negative nogo, (5) negative go, positive nogo, (6) negative go, neutral nogo. Each

block contained a pseudoranomized presentation of 30 go trials and 10 nogo trials, resulting in a total of 360 go trials and 120 nogo trials. To enable a parametric assessment of sequential facilatory and inhibitory processes, the number of go cues preceding nogo cues in the trial order was counterbalanced in all blocks from 0 to 6 according to previous studies (34). In each trial, words were presented for 280 ms followed by a fixation cross, which was used to reduce eye movements. The presentation time of the fixation cross was randomized from 1200 to 1400 ms to discourage anticipatory responses. Words were taken from the Berlin Affective Word List Reloaded (50) and were matched for number of letters, syllables, phonemes, frequency of appearance, number of orthographic neighbors and imageability. Furthermore, negative and positive words were matched for arousal but differed in valence ratings (Supplementary information).

2.3.6 Electroencephalogram recording

Electroencephalogram (EEG) recordings were made using Bio-Semi (Amsterdam, The Netherlands) ActiveTwo electrode system with 64 scalp electrodes. Additional electrodes were attached on the outer canthus of each eye to record the horizontal electrooculogram and infraorbitally and supraorbitally to the left eye to record the vertical electrooculogram. Electrophysiologic signals were digitized at 512 Hz.

2.3.7 EEG analysis

EEG data were high-pass filtered at 0.5 Hz to attenuate channel drifts. Bad channels were interpolated using spherical splines (51), and eye movements and blinks were removed by applying the extended infomax ICA algorithm (52,53). EEG data were low-pass filtered at 30 Hz. All trials (correct and incorrect) were segmented separately for each valance go/nogo combination from -200 to +1200 ms relative to stimulus presentation. To avoid remaining artifacts in further analysis, segments with activity exceeding ±75 µV in any channel, gradients of 50 µV/s and activity below 0.5 µV for at least 100 ms were excluded from further analysis before averaging. ERPs were rereferenced to the average reference before N2 and P300 amplitudes were quantified against baseline activity. Peak amplitudes were obtained from the 4 midline electrodes that revealed highest amplitudes across all drug conditions. The N2 was therefore defined as the most negative peak from 250–450 ms at electrode AFz, Fz, FCz, Cz, and the P300 was defined as the most positive peak from 450–700 ms at FCz, Cz, CPz, Pz (Figure S1 in Supplementary information).

2.4 Results

2.4.1 Acute subjective effects

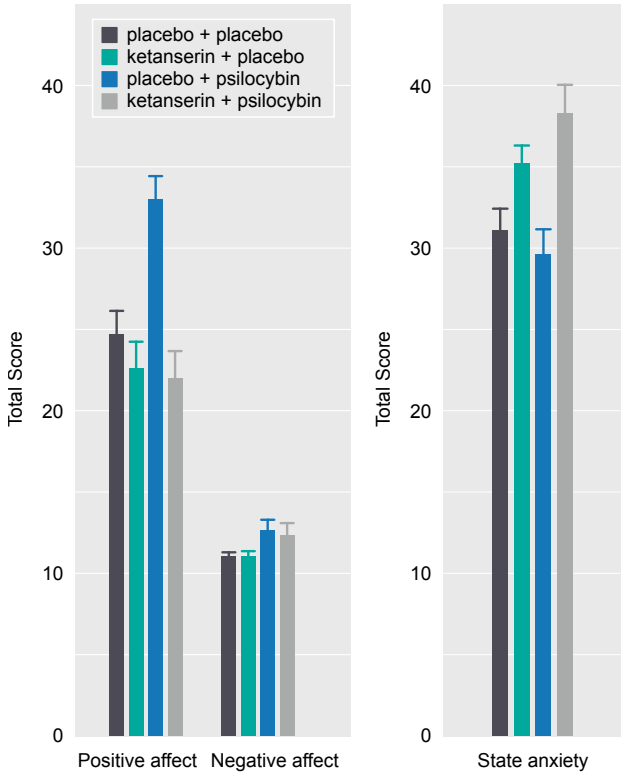
PANAS

Repeated-measures analysis of variance (ANOVA) with pretreatment, treatment and subscale as within-subject factors revealed that psilocybin significantly increased PANAS scores ($F(1,16)=16.608$, $p<0.001$, $\eta_p^2=0.509$). Importantly, the triple interaction between pretreatment × treatment × subscale ($F(1,16)=21.160$, $p<0.001$, $\eta_p^2=0.569$) showed that psilocybin significantly increased positive affect subscale after pretreatment with placebo ($p<0.00001$) but not ketanserin ($p=1$) (Figure 1). In contrast, psilocybin did not increase negative affect, neither after pretreatment with placebo ($p=1$) nor after pretreatment with ketanserin ($p=1$).

STAI-State

Repeated-measures ANOVA revealed a significant pretreatment × treatment interaction ($F(1,16)=14.708$, $p<0.01$, $\eta_p^2=0.480$). Bonferroni-corrected post-hoc analyses of this interaction indicated that ketanserin increased STAI scores in placebo- ($p<0.01$) and psilocybin-treated ($p<0.000001$) subjects. In contrast, psilocybin did not change STAI scores after pretreatment with placebo ($p=0.515$) (Figure 1).

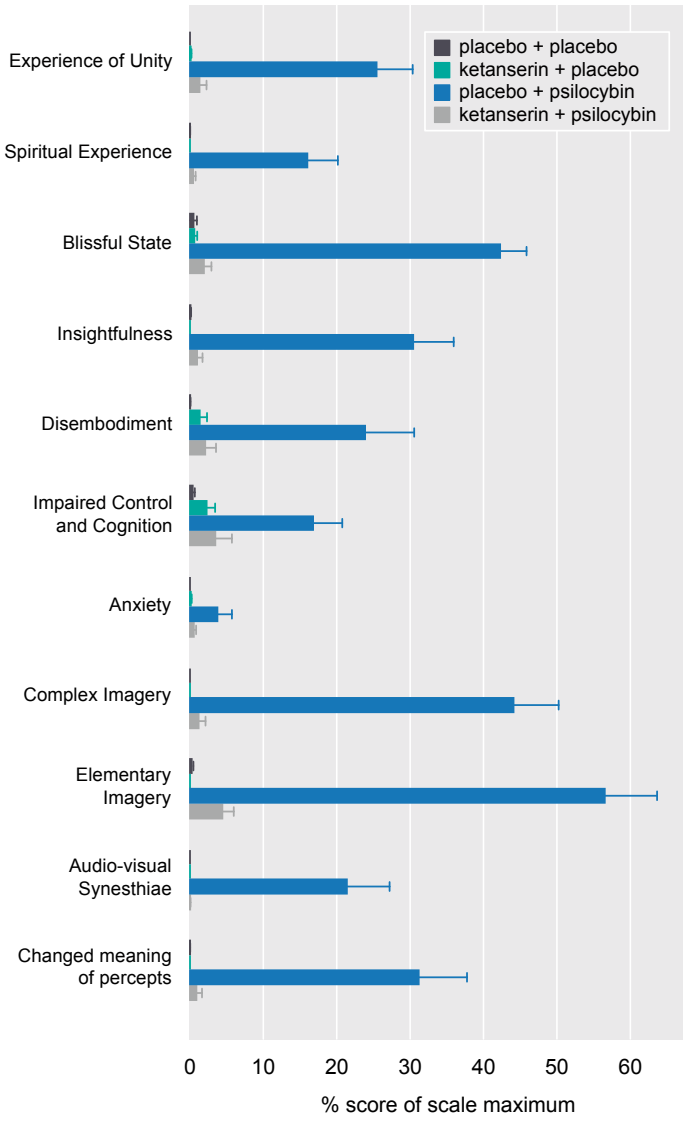
Figure 1
Subjective effects of psilocybin and ketanserin as measured by the positive and negative affect scale (PANAS) and the State-trait anxiety inventory (STAI). Values are the mean and standard errors of total scores.



5D-ASC

Psilocybin significantly increased 5D-ASC scores ($F(1,16)=78.059$, $p<1–6$, $\eta_p^2=0.823$) and pretreatment with ketanserin reduced this psilocybin-induced increase $F(1,16)=87.223$, $p<1–7$, $\eta_p^2=0.845$). Bonferroni-corrected post-hoc analysis on the triple interaction between pretreatment × treatment × subscale ($F(10,160)=9.549$, $p<1–11$, $\eta_p^2=0.374$) indicated that psilocybin increased the blissful state subscale, as well as the experience of unity, insightfulness, complex imagery, elementary imagery, changed meaning of percepts (all p's$<1–9$), the disembodiment ($p<1–8$), audio-visual synesthesiae ($p<0.00001$), impaired control and cognition ($p<0.001$), spiritual experience ($p<0.01$), but not Anxiety ($p=1$) subscale after pretreatment with placebo. Psilocybin did not increase any of these 11 subscales after pretreatment with ketanserin (all p's$=1$) (Figure 2).

Figure 2
Subjective effects of psilocybin as measured by the 5-Dimension Altered States of Consciousness scale (5D-ASC). Vales are the means and standard errors of percentages of the total possible scores of the eleven subscales of the 5D-ASC.



2.4.2 Facial emotional recognition

Error rate

A repeated-measures ANOVA using pretreatment, treatment and valence as within-subject factors revealed a main effect of valence ($F(2,32)=16.857$, $p<0.0001$, $\eta_p^2=0.513$). Psilocybin modulated error rates depending on the valence of the facial expression ($F(2,32)=5.460$, $p<0.01$, $\eta_p^2=0.254$). This interaction between treatment and valence was further modulated by pretreatment ($F(2,34)=3.886$, $p<0.05$, $\eta_p^2=0.181$) because psilocybin increased error rates for negative faces only after placebo ($p<0.05$) but not ketanserin pretreatment ($p=1$) (Figure 3). Overall, this interaction indicated a relative enhanced performance for positive compared to negative items particulary in the placebo + psilocybin condition ($p<0.00001$) and somewhat in the ketanserin + psilocybin condition ($p<0.01$), but not in the placebo + placebo ($p=0.44$) and ketanserin + placebo condition ($p=1$). A second repeated measure ANOVA on the valence of the choosen word using pretreatment and treatment as within subject factors revealed that psilocybin biased to choose higher valenced words ($F(1,16)=3.667$, $p=0.074$, $\eta_p^2=0.186$) and ketanserin lower valenced words ($F(1,16)=4.040$, $p=0.062$, $\eta_p^2=0.202$) at a trend level.

2.4.3 Emotional go/nogo task

Behavioral results

Reaction time (RT)

RTs for correct responses to go stimuli were subjected to a repeated-measures ANOVA using pretreatment, treatment and valence as within-subject factors. RTs were modulated by word valence ($F(2,32)=31.312$, $p<1–7$, $\eta_p^2=0.662$). Psilocybin increased RTs ($F(1,16)=9.696$, $p<0.01$, $\eta_p^2=0.378$) as a function of word valence ($F(2,32)=6.742$, $p<0.01$, $\eta_p^2=0.296$). Specifically, psilocybin increased reaction time much more for negative ($p<1–6$) and neutral ($p<1–7$) than for positive words ($p<0.01$), which indicates a stronger response bias to positive versus negative words in psilocybin ($p<1–6$) than in placebo condition ($p<0.05$) (Figure 4). Pretreatment with ketanserin did not significantly change this psilocybin-induced preferential reaction time for positive words ($F(2,32)=0.860$, $p=0.433$, $\eta_p^2=0.051$).

Error rate

A repeated-measures ANOVA on error rates with pretreatment, treatment, go/nogo, and valence as within-subject factors showed a main effect of valence ($F(2,32)=14.949$, $p<0.0001$, $\eta_p^2=0.480$) and go/nogo condition ($F(1,16)=25.001$, $p<0.001$, $\eta_p^2=0.610$). Psilocybin increased error rates ($F(1,16)=18.640$, $p<0.001$, $\eta_p^2=0.5381$) depending on word valence ($F(2,32)=3.624$, $p<0.05$,

Figure 3
Effect of psilocybin and ketanserin on error rates in recognizing positive, neutral and negative facial expressions. Values are the means and standard errors.

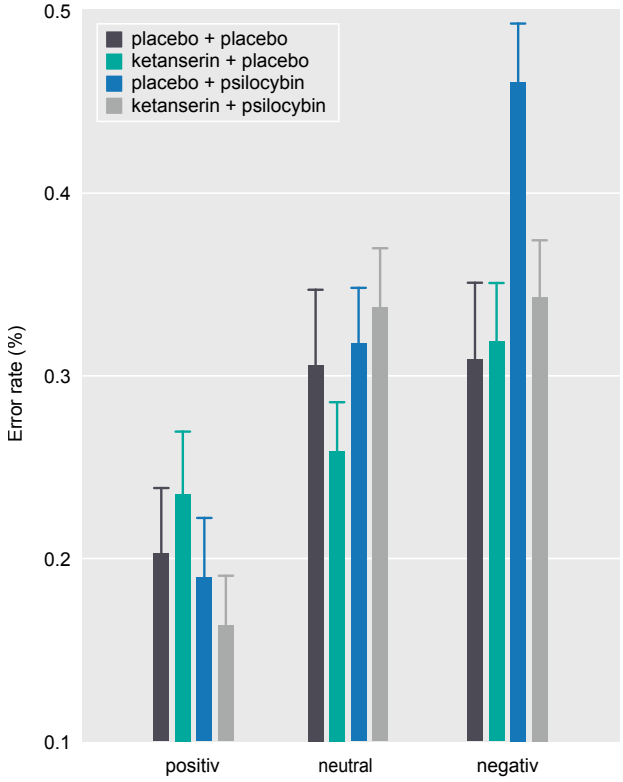


Figure 4
Effect of psilocybin and ketanserin on RTs towards positive, neutral and negative cues in the emotional go/nogo task. Values are the means and standard errors.

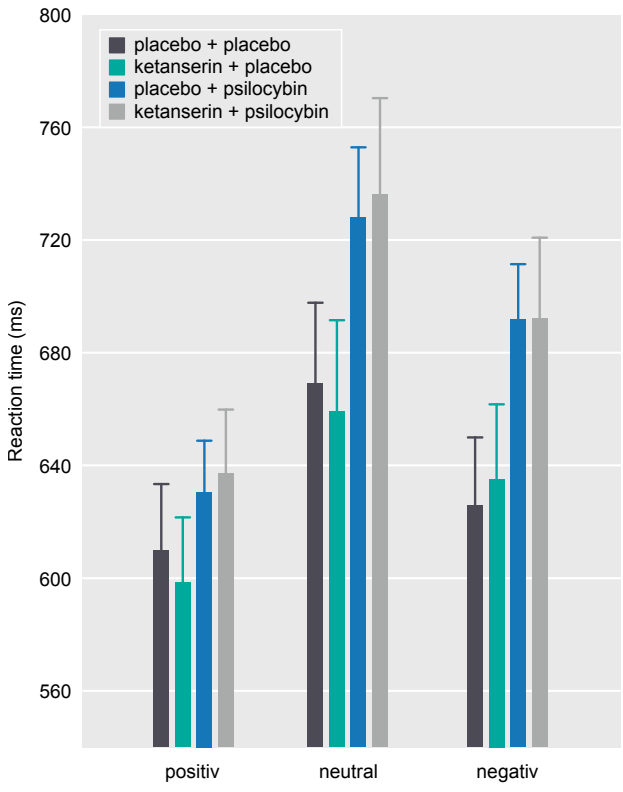
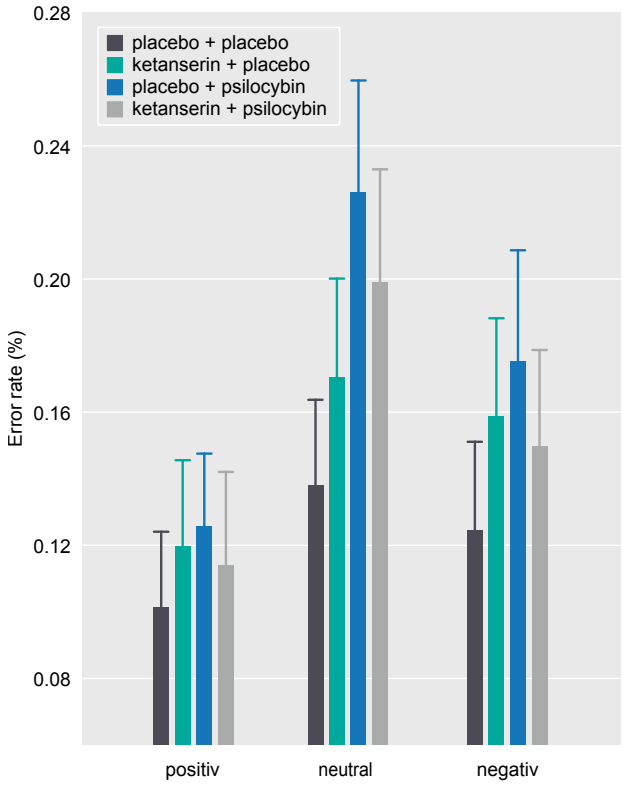


Figure 5
Effect of psilocybin and ketanserin on error rates in responding towards positive, neutral and negative cues in the emotional go/nogo task. Values are the means and standard errors



$\eta_p^2 = 0.185$), but irrespective of go/nogo condition ($F(1,16) = 0.112$, $p = 0.742$, $\eta_p^2 = 0.007$). Specifically, psilocybin significantly increased error rates only for neutral ($p < 0.01$) but not for positive ($p = 1$) or negative ($p = 1$) words (Figure 5). Furthermore, error rates were higher for negative compared to positive stimuli after psilocybin ($p < 0.05$) but not placebo administration ($p = 0.40$). These valence-specific effects of psilocybin on error rates did not differ between the go and nogo condition ($F(2,32) = 1.643$, $p = 0.209$, $\eta_p^2 = 0.093$) and were not altered by ketanserin pretreatment ($F(2,32) = 0.887$, $p = 0.422$, $\eta_p^2 = 0.053$).

Sequential effects

To assess sequential effects, RTs for correct responses to go stimuli were subjected to a repeated-measures ANOVA using pretreatment, treatment, valence and number of repetition as within-subject factors. RTs decreased with increasing number of repetition ($F(5,80) = 2.677$, $p < 0.05$, $\eta_p^2 = 0.143$), which was valence-specific ($F(10,160) = 5.501$, $p < 0.00001$, $\eta_p^2 = 0.256$). Subsequent Bonferroni-corrected post-hoc analyses showed that RTs to go stimuli was decreased for the sixth repetition (maximal repetition) of positive ($p < 0.01$) and neutral ($p < 0.01$) but not negative go stimuli ($p = 0.10$) compared to zero repetition (minimal repetition). Interestingly, psilocybin modulated these sequential emotional effects, which is indicated by the significant triple interaction between treatment × valence × number of repetition ($F(10,160) = 2.500$, $p < 0.01$, $\eta_p^2 = 0.135$).

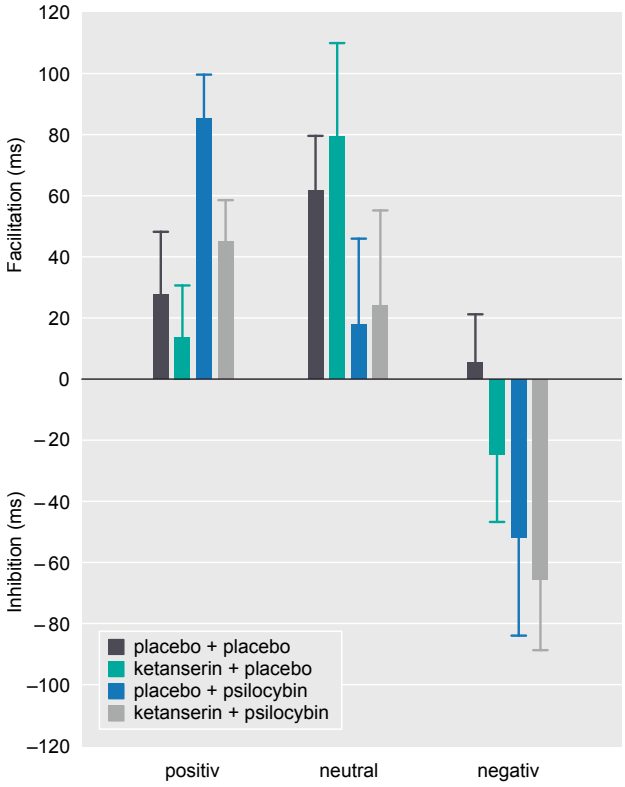


Figure 6
Effect of psilocybin and ketanserin on sequential emotional RT effects in the emotional go/nogo task. Depicted are differences in RTs (means and standard errors) between the conditions with minimal (zero repetition) and maximal repetitions (six repetitions) of positive, neutral and negative cues.

Specifically, the decrease in RTs between 0 and 6 repeating positive trials reached Bonferroni-corrected significance after treatment with psilocybin ($p < 0.001$) but not placebo ($p = 1$), while a significant increase of RTs between 0 and 6 repeating negative trials were observed after psilocybin ($p < 0.01$) but not placebo treatment ($p = 1$) (Figure 6).

Electrophysiological results

N2

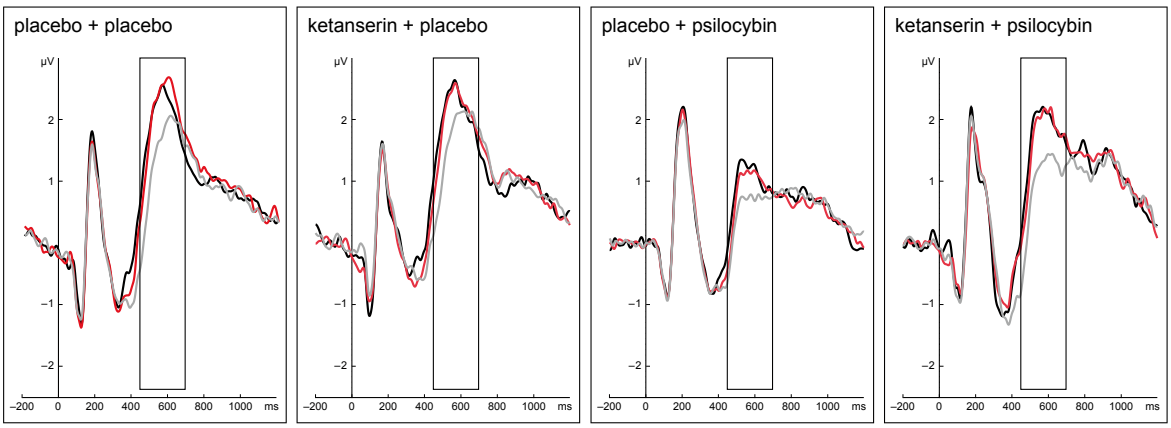
A repeated measures ANOVA on the N2 amplitude with pretreatment, treatment, go/nogo, valence and electrode as within-subject factors revealed higher N2 amplitudes for neutral compared to negative ($p < 0.05$) and positive ($p < 0.05$) stimuli ($F(2, 32) = 5.036$, $p < 0.05$, $\eta_p^2 = 0.239$) and higher amplitude for nogo compared to go stimuli ($F(1, 16) = 20.073$, $p < 0.001$, $\eta_p^2 = 0.556$). Psilocybin attenuated the N2 amplitude ($F(1, 16) = 5.230$, $p < 0.05$, $\eta_p^2 = 0.246$) independent of the word valence ($F(2, 32) = 2.538$, $p = 0.094$, $\eta_p^2 = 0.137$) and the go/nogo condition ($F(1, 16) = 0.701$, $p = 0.415$, $\eta_p^2 = 0.042$).

P300

A repeated measure ANOVA using pretreatment, treatment, go/nogo, valence and electrode as within-subject factors revealed higher P300 amplitudes for positive ($p < 1–6$) and negative

($p < 1–7$) compared to neutral stimuli ($F(2,32) = 29.740$, $p < 1–7$, $\eta_p^2 = 0.650$) and higher amplitudes for nogo than for go stimuli ($F(1,16) = 117.689$, $p < 1–8$, $\eta_p^2 = 0.880$). Psilocybin decreased the P300 amplitude ($F(1,16) = 15.323$, $p < 0.01$, $\eta_p^2 = 0.483$) depending on pretreatment condition ($F(1,16) = 4.646$, $p < 0.05$, $\eta_p^2 = 0.225$). Bonferroni-corrected post-hocs showed that psilocybin decreased the P300 amplitude only after pretreatment with placebo ($p < 0.01$) but not ketanserin pretreatment ($p = 1$). Importantly, the psilocybin-induced decrease was dependent on the word valence ($F(2,32) = 3.94$, $p < 0.05$, $\eta_p^2 = 0.198$) because the decrease was most pronounced for neutral ($p < 1–13$, -0.97 µV) followed by negative ($p < 1–12$, -0.85 µV) and positive ($p < 1–10$, -0.71 µV) words. The significant triple interaction between pretreatment × treatment × valence ($F(2,32) = 4.164$, $p < 0.05$, $\eta_p^2 = 0.207$) revealed the complex nature of the drug effects on the emotional processing. Specifically, during placebo+placebo condition Bonferroni-corrected post-hocs indicated higher P300 amplitudes for negative compared to neutral words ($p < 0.001$). In contrast in the placebo + psilocybin condition the positive stimuli evoked higher P300 amplitudes compared to neutral stimuli ($p < 0.05$). The strongest effect were seen in the ketanserin + psilocybin condition because P300 amplitude were much higher for positive ($p < 0.00001$) and negative stimuli ($p < 0.00001$) compared to neutral stimuli (Figure 7).

Figure 7
Effect of psilocybin and ketanserin on the group-averaged event related potential waveforms in response to positive (black traces), negative (red traces) and neutral stimuli (grey traces) averaged from FCz, Cz, CPz and Pz electrode sites, where P300 amplitude was most pronounced. The box indicates the time-range of the P300 component.



2.5 Discussion

Our data show that psilocybin biases emotional processing towards positive relative to negative information, an effect that is consistent across different psychological domains. Specifically, psilocybin first enhanced positive mood states, second decreased recognition of negative facial expression, and third increased behavior towards positive relative to negative cues. In contrast to these generalized effects of the serotonergic agonist psilocybin, a more specific role for 5-HT2A receptors in elevating mood and attenuating the recognition of negative facial expression is indicated by the finding that the preferential 5-HT2A antagonist ketanserin blocked these psilocybin-induced effects.

2.5.1 Mood states

Psilocybin predominantly enhanced positive mood states, as evidenced by the marked increase in the “positive affect” but not “negative affect” subscale scores of the PANAS questionnaire, as well as by the increase in “blissful” but not “anxiety” subscale scores of the 5D-ASC questionnaire. These strong effects of psilocybin on mood contrasts with the usually lacking acute mood effects of drugs that modulate the serotonergic tone such as acute tryptophan depletion (30, 35, 54) or selective serotonin reuptake inhibitors (SSRI) administration (31, 32, 55). This apparent disparity suggests that a specific activation of certain 5-HT subreceptors is necessary to acutely enhance mood. Indeed, the finding that the preferential 5-HT2A antagonist ketanserin blocked the mood enhancing effects of psilocybin suggests that 5-HT2A receptors are implicated in regulating positive mood states. Moreover, we argue that the additional stimulation of 5-HT1A or 5-HT2C receptors by psilocybin is rather unlikely to contribute to the mood effects of psilocybin, because ketanserin has nearly no affinity to 5-HT1A receptors and about 50 fold higher affinity to 5-HT2A compared to 5-HT2C receptors (Psychoactive Drug Screening Program [PDSP]: http://pdsp.med.unc.edu). Furthermore, the 5-HT2B/2C agonist meta-Chlorphenylpiperazin (mCPP) induces anxiety rather than positive mood states (56). Finally, it is unlikely that expectation of receiving psilocybin considerably contributed to the mood effects, because various drug combinations were administrated in a double-blind procedure and subjects were instructed that the psychological effects of psilocybin varies largely between and within subjects.

2.5.2 Facial emotional recognition

Serotonin 2A receptors appear also to be crucially involved in the recognition of negative facial expressions, because ketanserin blocked psilocybin-induced attenuation in recognizing negative

emotional states from the eye region of human faces. This finding is in line with the central role of serotonin in emotional facial recognition as previously established by pharmacological (29–33) and genetic studies (57), but extends this notion by showing that specific activation of 5-HT2A receptors likely biases facial recognition away from negative emotion. This mechanism might also contribute to the attenuated recognition of negative facial expression as previously observed after single dose of 3,4-Methylenedioxymethamphetamine (MDMA)(33) and after chronic administration of SSRIs (29, 58), because MDMA has a moderate affinity at 5-HT2A receptors (59) and chronic SSRI administration changes 5-HT2A receptor density (60, 61).

2.5.3 Goal-directed behavior

In the emotional go/nogo task psilocybin enhanced the response bias towards positive relative to neutral and negative emotional stimuli, which was evidenced at the behavioral level by the psilocybin-induced increase in reaction times to negative and neutral compared to positive stimuli. In addition, this response bias was modulated by the sequential context of the stimuli across all drug conditions, an effect that was augmented by psilocybin administration. That is, across all drug conditions sequential repetition of positive and neutral stimuli facilitated processing (62, 63), as indicated by decreased reaction times to positive and neutral stimuli. Interestingly, this sequential facilatory effect was lacking after negative stimuli, a finding that has not yet been reported in emotional go/nogo tasks but was previously observed in semantic (64, 65) and negative affective priming tasks (66–68). Given that this lacking facilitation has been interpreted as an inhibition of negative concepts within the attentional (66) or memory system (65), and that psilocybin prolonged reaction time for repeated negative stimuli but decreased it for repeated positive stimuli, psilocybin may also increase inhibition of negative relative to positive concepts in the attentional or memory system.

Support for such a psilocybin-induced shift in the attentional system was revealed by the effect of psilocybin on event-related potentials. The event-related potentials analysis indicated that across all drug conditions, the word valence affected early and late response-selection, inhibition and attention processes as indexed by the decreased N2 and enhanced P3 component for emotional relative to neutral stimuli (69, 70). Most importantly, while psilocybin and ketanserin did not modulate these valence-specific effects during the N2 time-range, psilocybin strongly decreased the P300 component in all valence conditions, and particularly for negative and neutral stimuli. Because this valence-dependent P300 decrease was equally present in both the go and nogo condition, it is conceivable that this psilocybin-induced change in emotional processing is neither specific for response selection (go) nor for inhibition (nogo), but rather reflects a more general process underlying the P300. For instance, the P300 amplitude is strongly modulated by the amount of attentional resource allocation (71), and several behavioral studies previously

showed that psilocybin attenuates attentional performance (41, 72, 73). This suggests on the one hand that the strong psilocybin-induced decrease of the P300 seen across all valence conditions might reflect an important electrophysiological index of the previously reported psilocybin-induced attentional deficits. On the other hand, the small valence-dependent decrease suggests that psilocybin may attenuate the allocation of attentional resources to neutral and negative stimuli more strongly than to positive stimuli, which results in a relative positive attentional bias.

Contrary to the crucial contribution of 5-HT2A receptors in modulating mood states and emotional face recognition, the psilocybin-induced relative bias towards the processing of positive emotions in the go/nogo task were not blocked by pretreatment with ketanserin. Thus the psilocybin-induced emotional bias might rather be due to a stimulation of 5-HT1A or 5-HT2C receptor than 5-HT2A receptors. However, the strong valence-independent reduction of the P300 seen after psilocybin administration was partially reversed by ketanserin, indicating an involvement of 5-HT2A receptors in the valence-independent attentional performance.

2.5.4 Implication for mood disorders

In the present study psilocybin produced behavioral and electrophysiological effects that were opposite to the dysfunctional emotional processing bias seen in depressed subjects in emotional facial recognition (1, 29–31), goal-directed behavior (2, 3, 70) and mood states. For example, in the emotional go/nogo task psilocybin increased RTs and decreased P300 amplitudes particulary for negative and neutral stimuli, while depressed subjects were delayed in responding to positive cues (2, 3) and displayed increased P300 component for negative stimuli (70). Thus it appears that psilocybin may have the potential to acutely shift dysfunctional emotional biases in depression. Such an acute shift might in conjunction with the reported effect of psilocybin on neuroplastic factors (24) lead to sustained adaptations and may therefore account for the discussed antidepressive potential of psilocybin-like compounds (24, 28). Hence, further studies using different and multiple doses of psilocybin are indicated to explore, whether the effect of psilocybin on emotional biases are dose-dependent and whether psilocybin may shift the negative emotional biases seen in depression.

Furthermore, here we identify 5-HT2A receptors activity as a potential crucial pharmacological target in the treatment of negative mood states and negative emotional facial recognition bias. In line with this finding, negative mood is associated with pessimistic attitudes (74) and medication-free major depression patients with high pessimistic attitudes have increased 5-HT2A receptor binding in the prefrontal cortex compared to healthy controls (8–10). Furthermore, chronic administration of SSRIs does not only shift negative mood states and negative bias in facial recognition in depressed patients (29, 58) but also seems to normalize alterations in 5-HT2A receptor densities in depressed subjects (60, 61).

In sum, the present study indicates that the assessment of the effects of psilocybin provides a valuable framework to identify neuropsychopharmacological mechanisms underlying dysfunctional emotional biases and the putative antidepressant effects of psilocybin and related compounds.

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2.9 Supplemental Information

Supplemental Methods

Study on the "Reading the Mind in the Eyes Test"

In a study involving 40 subjects (20 men, 20 female, mean age 27) the 36 pictures were presented without target and distracter words and subjects rated the picture on the 9-point Self-Assessment Manikin (SAM) scale (1). These rating scores were subjected to a one-sample t-test. Pictures with ratings significantly ($p<0.05$) below neutral (=5) were categorized as negative and pictures and ratings significantly ($p<0.05$) above neutral as positive, while pictures that did not reach significance belonged to the neutral category. Additionally, all words (target and distracters) were presented on a second occasion without pictures and subjects rated the words using again the SAM scale. These values were used to assess whether the valence of the chosen word was significantly modulated by the pharmacological manipulations.

Table S1. Ratings of the "Reading the Mind in the Eyes Test"

Item No.	Valence	Rating Score	Standard Deviation	Standard Error	t-value	p
2	negativ	2.275000	1.085747	0.171672	-15.8733	0.000000
26	negativ	2.725000	1.300641	0.205649	-11.0625	0.000000
8	negativ	3.125000	1.380960	0.218349	-8.5872	0.000000
32	negativ	3.475000	1.552294	0.245439	-6.2134	0.000000
22	negativ	3.475000	1.518898	0.240159	-6.3500	0.000000
35	negativ	3.475000	1.154423	0.182530	-8.3548	0.000000
5	negativ	3.600000	1.428645	0.225889	-6.1977	0.000000
33	negativ	3.725000	1.449801	0.229234	-5.5620	0.000002
14	negativ	4.000000	1.414214	0.223607	-4.4721	0.000065
17	negativ	4.075000	1.308503	0.206892	-4.4709	0.000065
4	negativ	4.400000	0.955416	0.151065	-3.9718	0.000298
23	negativ	4.550000	1.060962	0.167753	-2.6825	0.010661
31	neutral	4.575000	1.646870	0.260393	-1.6321	0.110698
9	neutral	4.675000	1.227620	0.194104	-1.6744	0.102062
24	neutral	4.675000	1.558887	0.246482	-1.3186	0.195009

29	neutral	4.675000	1.474353	0.233116	-1.3942	0.171163
27	neutral	4.700000	1.362501	0.215430	-1.3926	0.171642
18	neutral	4.775000	1.790108	0.283041	-0.7949	0.431461
19	neutral	4.775000	1.458617	0.230628	-0.9756	0.335276
11	neutral	4.775000	1.761228	0.278475	-0.8080	0.424007
28	neutral	4.875000	1.635935	0.258664	-0.4833	0.631619
36	neutral	4.875000	2.065436	0.326574	-0.3828	0.703975
7	neutral	4.975000	1.404891	0.222133	-0.1125	0.910968
34	neutral	5.075000	1.926702	0.304638	0.2462	0.806824
12	neutral	5.175000	1.430214	0.226137	0.7739	0.443675
13	neutral	5.225000	1.731866	0.273832	0.8217	0.416259
25	neutral	5.375000	1.563814	0.247261	1.5166	0.137428
16	positiv	5.600000	1.104768	0.174679	3.4349	0.001420
10	positiv	5.675000	1.347124	0.212999	3.1690	0.002972
30	positiv	5.900000	1.549193	0.244949	3.6742	0.000715
3	positiv	6.075000	1.327954	0.209968	5.1198	0.000009
15	positiv	6.100000	1.410583	0.223033	4.9320	0.000016
6	positiv	6.200000	1.264911	0.200000	6.0000	0.000001
21	positiv	6.250000	1.372813	0.217061	5.7588	0.000001
1	positiv	6.275000	1.484752	0.234760	5.4311	0.000003
20	positiv	6.800000	1.223698	0.193484	9.3031	0.000000

Table S2. Characteristics of affective words in the go/nogo task

	positiv	negativ	neutral
Number of letters	6.4 ± 1.5	6.3 ± 1.5	6.6 ± 1.4
Syllables	2.1 ± 0.7	2.0 ± 0.7	2.2 ± 0.6
Phonems	5.7 ± 1.4	5.6 ± 1.5	5.8 ± 1.4
Frequency of appearance per million words	50.4 ± 57.5	40.2 ± 65.5	48.7 ± 83.5
Number of orthographic neighbors	1.5 ± 2.2	1.6 ± 2.2	2.1 ± 2.6
Imageability	4.1 ± 1.2	3.9 ± 1.0	3.4 ± 1.3
Arousal	3.2 ± 0.6	3.5 ± 0.6	1.9 ± 0.3
Valence	2.2 ± 0.3	-2.1 ± 0.3	0.0 ± 0.3

Electroencephalography Analysis

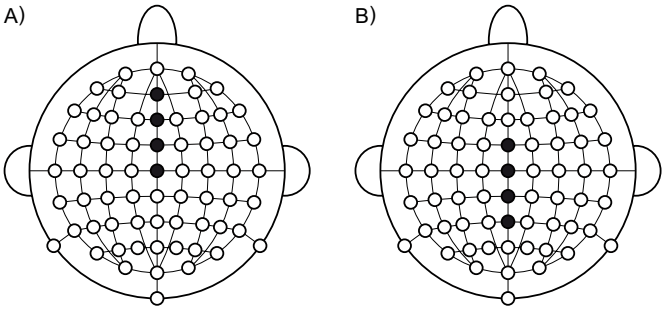

Figure S1. Display of the scalp electrode sites used in the event-related potential analyses. **A)** Highlighted in black are the electrodes AFz, Fz, FCz and Cz that were used for the N2 peak measurements. **B)** Highlighted in black are the electrodes FCz, Cz, CPz and Pz that were used for the P300 peak measurements.

Supplemental Results

Differences between go and nogo condition in the N2 and P3 scalp topography

Repeated measure analysis of variance (ANOVA) on the N2 amplitude revealed no significant interaction between electrode and go/nogo condition ($F(3,48)=0.959$, $p=0.420$, $\eta_p^2=0.057$) and no significant triple interaction between electrode × go/nogo condition × treatment ($F(3,48)=0.662$, $p=0.580$, $\eta_p^2=0.040$). However, repeated measure ANOVA on the P300 amplitude revealed a significant interaction between electrode and go/nogo condition ($F(3,48)=27.336$, $p<1–9$, $\eta_p^2=0.631$), indicating that the nogo compared to the go stimuli induced a more anterior P300 distribution. Psilocybin did not modulate this topographic difference because the interaction between electrode × go/nogo condition × treatment did not reach significance ($F(3,48)=0.245$, $p=0.865$, $\eta_p^2=0.015$).

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3

The 5-HT2A/1A agonist psilocybin disrupts modal object completion associated with visual hallucinations

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Personal contribution

M. K. conceived and designed the study, developed the task, and gathered and analyzed all behavioral and EEG data, interpreted the data and wrote the paper. F. X. V., R. B. C., D. A., O. L. C. helped to conceive and design the study, gather the data, interpret the data and/or revise the first draft of the paper.

3.1 Abstract

Background

Recent findings suggest that the serotonergic system and particularly the 5-HT2A/1A receptors are implicated in visual processing and possibly the pathophysiology of visual disturbances including hallucinations in schizophrenia and Parkinson's disease.

Methods

To investigate the role of 5-HT2A/1A receptors in visual processing the effect of the hallucinogenic 5-HT2A/1A agonist psilocybin (125 µg/kg and 250 µg/kg vs placebo) on the spatiotemporal dynamics of modal object completion was assessed in normal volunteers (n = 17) using visual evoked potential (VEP) recordings in conjunction with topographic-mapping and source-analysis. These effects were then considered in relation to the subjective intensity of psilocybin-induced visual hallucinations quantified by psychometric measurement.

Results

Psilocybin dose-dependently decreased the N170 and, in contrast, slightly enhanced the P1 component selectively over occipital electrode sites. The decrease of the N170 was most apparent during the processing of incomplete object figures. Moreover, during the time period of the N170 the overall reduction of the activation in the right extrastriate and posterior parietal areas correlated positively with the intensity of visual hallucinations.

Conclusions

These results suggest a central role of the 5-HT2A/1A-receptors in the modulation of visual processing. Specifically, a reduced N170 component was identified as potentially reflecting a key process of 5-HT2A/1A receptor-mediated visual hallucinations and aberrant modal object completion potential.

3.2 Introduction

Despite the fact that the visual and serotonergic systems are among the most explored research topics in neuroscience, there is sparse information about the role of serotonin (5-HT) in visual processing. However, the high expression of the 5-HT1A (1, 2) and 5-HT2A receptors (3–5) in the visual areas V1, V2, V3 and lateral suprasylvian cortex (LS) suggest a central role of the 5-HT1A and 2A receptors in visual processing. Furthermore, 5-HT2A receptors have been implicated in the pathogenesis of visual hallucinations in Parkinson's (6–8) and schizophrenic patients (9). In support

of this view, visual hallucinations in Parkinson's patients have been associated with increased density of 5-HT2A receptors in cortical visual pathways (6, 8) and effectively treated with the 5-HT2A receptor inverse agonist pimavanserin (7). Moreover, visual disturbances and hallucinations induced by the indoleamine hallucinogen psilocybin are predominantly mediated by the 5-HT2A receptor (10) and resemble, in phenomenological (11) and behavioural measurements (12), visual disturbances found in schizophrenia (13, 14). Hence, there is an increasingly recognized role for the 5-HT2A receptors in the pathogenesis of visual hallucinations, while the brain mechanisms mediating between 5-HT2A receptor activation and visual hallucination are still unknown.

To further characterize the role of the 5-HT2A/1A receptors in visual processing and to elucidate possible pathophysiological mechanisms of visual deficits and hallucinations, we assessed the effect of the mixed 5-HT2A/1A agonist psilocybin (125 µg/kg and 250 µg/kg vs. placebo) in healthy volunteers. Electroencephalographic recordings were made while participants viewed Kanizsa- and non-Kanizsa-figures (Figure 1). Behavioural responses were recorded and high-density electrical mapping with source-analysis was used. This allowed for measurement of the spatiotemporal brain dynamics of visual modal object completion and its association with the appearance of visual hallucinations.

Modal object completion refers to the illusory perception of object boundaries and their enclosing surface in the absence of any direct sensory information depicting these boundaries or surfaces. The brain's ability to interpolate the existence of object surface boundaries is essential for accurate object recognition in situations where only ambiguous or incomplete retinal information of the object is available (i. e. due to partial occlusion or poor illumination). Modal completion has been of particular interest to vision scientists as it is critical for the accurate perception of objects and the delineation of multiple objects from themselves or their background. Imaging studies provide strong evidence that the intermediate lateral occipital complex (LOC) as well as the early visual area V2 are likely to play a major role in modal completion (15–18), while the involvement of the primary visual cortex is more contentious (19). Electrophysiological studies revealed that modal object completion of simple figures such as Kanizsa-figures is predominantly indexed by the modulation of the N170 component (20–25), which appears to be driven primarily by the two critical processes underlying modal object completion, boundary-completion (22) and region-based-segmentation (25). In some previous studies the presentation of Kanizsa-figures, compared to control figures, have additionally been associated with an enhancement of the earlier P1 (26) and the subsequent closure negativity (N_{cl}) component (22). However, as the N_{cl} component is more reliably induced by more complex fragmented images and reflects successful recognition of complex images (27, 28) it is unlikely to be as relevant to the processing of the simple Kanizsa-figures used in the current experiment.

The high density of 5-HT1A (1, 2) and 5-HT2A (3–5) receptors in LOC and V2, as well as the strong activation seen in these areas after psilocybin administration during resting state (29)

suggest that psilocybin might influence modal object completion. As these processes are so critical in defining one's perceptual experience, this study aims to characterize and understand the means by which 5-HT2A/1A receptor activity can alter this fundamental aspect of visual experience.

3.3 Methods and materials

3.3.1 Subjects

Healthy right-handed subjects (8 males, 9 females, mean age 28.8 ± 3.5 years) were recruited through advertisement from the University of Zurich. All subjects were healthy according to physical examination including electrocardiography, hematogram and detailed blood analysis. The DIA-X diagnostic expert system (30) and a clinical interview was used to exclude subjects with present or antecedent psychiatric disorders, regular alcohol or substance abuse and a history of major psychiatric disorders in first degree relatives. The screening procedure was supplemented by the Freiburg Personality Inventory FPI (31) and Hopkins Symptom Checklist SCL-90-R (32) and a self made substance consumption questionnaire. Since the personality trait factor "emotional lability" was identified to be a predictor for negative experiences during hallucinogen-induced altered states of consciousness (33), scores exceeding the mean value of normative FPI data by two SD were also used as exclusion criterion. Twelve participants reported having previous experience with psilocybin or other hallucinogens (mean life time experiences 5.5 ± 4.7 times). None of the subjects consumed any psychoactive substance except alcohol, nicotine, cannabis and caffeine more than once a year.

After being informed by a written and oral description of the procedures of the study and the effects and possible risks of PY administration, all volunteers gave written informed consent to participate in this study. The study was approved by the ethics committee of the University Hospital of Psychiatry, Zurich, and the use of psilocybin in humans was authorized by the Swiss Federal Office for public health.

3.3.2 Substance and dosing

Psilocybin was obtained through the Swiss Federal Office for Public Health. The psilocybin high-dose (HD, 250 µg/kg), low-dose (LD, 125 µg/kg), and lactose placebo (PL) were administered in gelatine capsules of identical number and appearance. On three experimental days, separated from each other by at least two weeks, the subjects came to the lab at 9 am and confirmed they had not eaten breakfast or taken caffeine that morning. In a cross-over randomised design, all subjects received placebo and the two graded doses of psilocybin.

3.3.3 Stimulus and procedure

The Kanizsa experiment started 120 min post-drug ingestion. During the experiment Kanizsa-figures and control figures were presented at a distance of 1 meter from the participants while they remained fixated on a central fixation-cross. All stimuli consisted of three “pacmen”, each composed of a black circle with a sector of 60 degrees removed. The removed sectors were either aligned such that the stimulus types induced the perception of an illusory triangle or they were rotated by 180 degrees so as to no longer induce the illusory triangle percept (‘Kanizsa’ and ‘non-Kanizsa’ conditions respectively; see Figure 1). The stimuli subtended a visual angle of 3.7° and the support ratio, the ratio of the inducing length to the total length of one illusory contour of the triangle, was 1:2. In order to reduce habituation, the stimuli were presented in four different orientations of equal number, rotated 0°, 90°, 180°, and 270°.

A total of 88 Kanizsa-figures and 88 non-Kanizsa-figures were presented with a stimulus onset asynchrony (SOA) of 3 seconds in a pseudorandomized order in two blocks consisting of 44 Kanizsa-figures and 44 non-Kanizsa-figures each. Participants were required to respond, as quickly as possible, with a button press according to whether or not they saw an illusory triangle on each trial. The response finger was counterbalanced across the subjects to control for faster reaction times of index finger compared to middle finger of the dominant hand. Stimuli remained on the monitor for 300 msec after button-press or for a maximum of 2000 msec.

3.3.4 Psychometry

The Altered States of Consciousness (5D-ASC) rating scale (34) was used to asses the subjective effects of placebo and psilocybin with a primary focus on visual alterations and hallucinations. The 5D-ASC is a visual-analogue scale consisting of 94 items that measure etiology independent alterations in consciousness, including changes in mood, perception, cognition and experience of self and of the environment. The five main factors are: (1) Oceanic Boundlessness, measuring derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria, and alterations in the sense of time. (2) Anxious Ego Dissolution measuring ego-disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. (3) Visionary Restructuralization (VR) assessing visual illusions and (pseudo-) hallucinations, which includes the whole spectrum ranging from elementary to complex hallucinations. (4) Auditory Alterations (AA) comprising auditory illusions and (pseudo-) hallucinations. (5) Reduction of Vigilance assessing changes in vigilance and alertness. The results of the 5D-ASC data are given as percentage scores of maximum absolute scale values.

3.3.5 EEG recording

EEG recordings were made using BioSemi ActiveTwo electrode system with 64 scalp electrodes. Additional electrodes were attached on the outer canthus of each eye to record the horizontal electrooculogram (EOG) and infraorbitally and supraorbitally to the left eye to record the vertical EOG. Electrophysiological signals were band-pass filtered at 0.01–67 Hz and digitized at 256 Hz.

3.3.6 EEG analysis

EEG data were recalculated offline against average reference and band-pass filtered at 1–40 Hz. Correct response trials were segmented from -150 to +600 ms relative to stimulus presentation. To avoid eye movement and other artifacts in further analysis, epochs exceeding ±100 µV in any channel were excluded. The mean ± SD number of accepted epochs per condition was 85.0 ± 5.4 for Kanizsa placebo, 85.0 ± 3.0 for non-Kanizsa placebo, 82.9 ± 4.6 for Kanizsa low-dose, 83.2 ± 3.7 for non-Kanizsa low-dose, 78.8 ± 9.4 for Kanizsa high-dose, 79.4 ± 9.8 for non-Kanizsa high-dose. These epochs were averaged time-locked to Kanizsa- and non-Kanizsa-figure presentation time to compute the VEP. The 600 ms poststimulus period of the VEP underwent three different analyses to reveal the VEP waveforms, the scalp topography and the source localization. This combination of analysis methods has been increasingly used during the last years, as it reduces experimenter bias associated with the selection of the appropriate time window for statistical analysis of the components (35).

Waveform analysis

To quantify waveform modulations, five symmetrical pairs of electrodes were selected over the maxima of the scalp topographies for the P1 and N170 components (PO7/PO8, PO3/PO4, O1/O2, P1/P2, P3/P4). The specific time windows used for calculation of the mean amplitude (versus the baseline) were determined by the topographic analysis described below. The mean amplitudes of each of these time windows were then subjected to separate repeated measures analysis of variance (ANOVA) with the within-subject factors dose (PL, LD, HD) electrode (PO7/PO8, PO3/PO4, O1/O2, P1/P2, P3/P4), hemiscalp (left, right) and stimulus (Kanizsa, non-Kanizsa).

Topographic analysis

First a spatial k-means cluster analysis identified the predominant topographies (also called template map) appearing in the normalized group-averaged ERPs as a function of time and experimental condition (36). This analysis was constrained by the temporal criterion, that certain topographies must be observed for at least 5 consecutive data points (>20 ms at a 256 Hz sampling rate). The optimal number of topographies that explained the whole dataset was deter-

mined by a modified cross-validation criterion (36). In a second step we statistically verified that maps identified at the group-averaged level also appeared on the individual subject level. Therefore, at each time point the topography of the individual subjects' ERP was compared by means of strength-independent spatial correlation to all template maps and was labeled according to the one with which it best correlated (35, 37). This revealed values of relative map presence (in milliseconds), which were then subjected to a repeated measures ANOVA using stimulus condition, map and dose as within-subject factors.

Source Localization

Standardized low-resolution electromagnetic tomography (sLORETA) was used to estimate the three dimensional intra-cerebral current density distributions underlying the ERPs within the time frames defined by topographic analysis. sLORETA offers a solution of the inverse problem by assuming that the smoothest of all possible activity is the most plausible one (38). The solution space of sLORETA (i.e. the lead field matrix) includes 6239 voxels and was computed with a three-shell spherical head model registered to the neuroanatomical atlas of Talairach and Tournoux (Brain Imaging Centre, Montreal Neurological Institute).

Correlational analyses

Correlational analyses were performed to determine whether psilocybin-induced changes in the current source density within the time frames defined by topographic analysis were related to visual or auditory hallucinations. First, the differences of the current source density between psilocybin conditions (low- and high-dose) and placebo were calculated separately. In a second step these data were pooled and the product-moment correlations between these differences and the VR and AA scores, respectively, were calculated for each voxel. Significant correlations were identified using nonparametric permutation testing (39) that determined the critical probability threshold values for the observed r-values with correction for multiple testing.

3.4 Results

3.4.1 Psychometrics

The subjective effects of psilocybin were assessed by the 5D-ASC rating scale. Repeated measures ANOVA revealed a significant main effect of dose ($F(2,32)=36.596$, $p<0.00001$, $\eta^2=0.70$), factor ($F(4,64)=12.924$, $p<0.00001$, $\eta^2=0.45$) and dose × factor interaction ($F(8,128)=7.09$, $p<0.00001$, $\eta^2=0.31$) . Bonferroni-corrected post-hoc analysis on the VR factor, which was of primary interest in regard to the current study, indicated a significant increase between placebo and low-dose psilocybin

($p<0.00001$) as well as placebo and high-dose psilocybin ($p<0.00001$) but not low-dose and high-dose psilocybin ($p=0.178$). Bonferroni-corrected post-hoc analysis on the AA factor revealed a significant increase between placebo and high-dose psilocybin ($p<0.05$) but not placebo and low-dose psilocybin ($p=1.0$).

3.4.2 Behavioral data

Reaction time was dose-dependently increased by psilocybin ($F(2,32)=18.841$, $p<0.00001$, $\eta^2=0.54$) and was generally faster for Kanizsa- compared to non-Kanizsa-figure ($F(1,16)=36.037$, $p<0.0001$, $\eta^2=0.69$) (Table 1). While psilocybin administration did lead to a dose-dependent increase in error rates ($F(2,32)=3.3291$, $p<0.05$, $\eta^2=0.17$), the error rates remained very low in all conditions (0.88% for placebo, 1.18% for low-dose, 1.92% for high-dose). We are therefore confident that participants were able to do the task under all drug conditions.

Table 1. Behavioral Results Corresponding to Kanizsa and Non-Kanizsa Condition for Placebo, Low-Dose, and High-Dose Psilocybin Expressed as Mean (SD)

	Kanizsa	Non-Kanizsa
Placebo		
Reaction time (msec)	514 (75)	538 (85)
Error rate (%)	.88 (.93)	.88 (1.36)
Low-dose		
Reaction time (msec)	544 (65)	583 (71)
Error rate (%)	1.47 (1.59)	.88 (1.54)
High-dose		
Reaction time (msec)	592 (79)	645 (72)
Error rate (%)	1.59 (1.42)	2.24 (3.17)

3.4.3 Electrophysiological data

Under all 3 drug conditions both stimuli elicited prominent VEP, including the P100 and N170 component (Figure 1) with a maximum over lateral occipital scalp areas (Figure 3). The subsequent topographic analysis detected nine different scalp topographies, which accounted for the 600 ms post-stimulus periods across all conditions with a global explained variance (GEV) of 96.74%. The first three time periods of stable scalp topographies were identical across conditions lasting from 0–86 ms, 90–144 ms, 148–223 ms (Supplementary Figure S1). These time periods were used to define the time window for quantifying the P1 and N170 VEP in a more objective manner (Murray et al., 2008) and for the subsequent source localization and correlation analysis (Analysis referring to the P300 component can be found in supplementary material).

P1

During the time-range of the P1 component (90–144 ms) a 3 × 2 × 5 × 2 repeated measures ANOVA (using dose, hemiscalp, electrode, and stimulus as within factors) revealed only a main effect of electrode ($F(4,64)=33.42$, $p<0.00001$, $\eta^2=0.68$) and a significant interaction of electrode and dose ($F(8,128)=3.43$, $P<0.01$, $\eta^2=0.18$). Performing bonferroni-corrected post-hoc analysis of this interaction, the P1 amplitude was found to be significantly increased from placebo only at the O1/O2 electrodes by low dose ($p<0.05$) and high dose ($p<0.0001$) psilocybin. No effect of psilocybin was observed at other electrodes, nor did any other interaction reach significance. This result indicates that the effect of psilocybin on the P1 component is locally restricted to occipital electrode sites and is independent of hemiscalp and stimulus condition (Figure 2). Furthermore, neither the main effect for dose ($F(2,32)=0.95$, $p=0.39$, $\eta^2=0.06$), stimulus ($F(1,16)=0.77$, $p=0.39$, $\eta^2=0.05$) nor hemiscalp ($F(1,16)=1.71$, $p=0.21$, $\eta^2=0.10$) reached significance.

To further elucidate topographic modulation of the P1 component, the spatial correlation procedure was used first to assess the number of time frames a given topography from the group-averaged data was present in a given condition across subjects (see methods). These values were subjected to a repeated measures ANOVA (using dose, stimulus, and map as within factors), which provided no evidence of topographic specificity to one stimulus or dose condition (all P's>0.15).

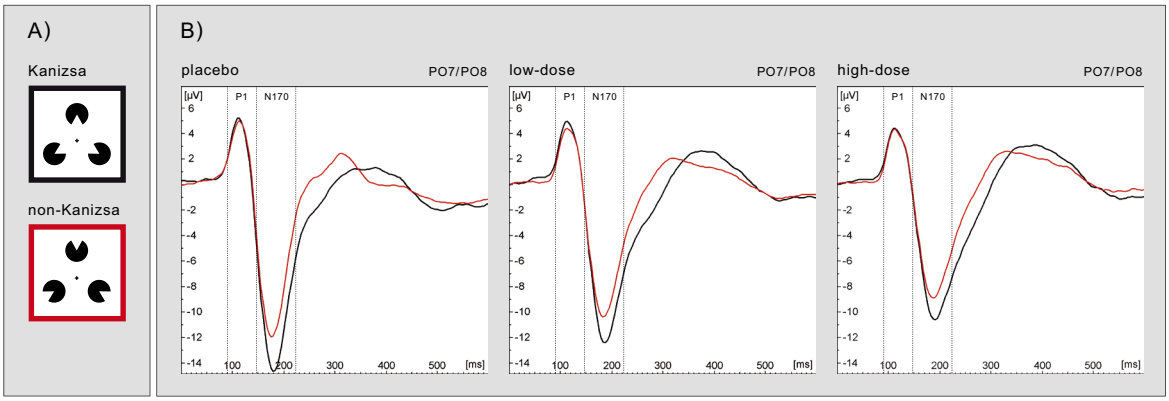

Figure 1

A) Example of Kanizsa-figure and non-Kanizsa-figure.

B) Group-averaged VEP waveforms in response to Kanizsa-figures (black traces) and non-Kanizsa-figures (red traces) for placebo, low-dose and high-dose condition averaged from the left and right posterior electrode sites PO7/PO8, where P1 and N170 amplitude was most pronounced. Dashed lines indicate the time period of stable topographic configuration of the P1 and N170 component.

Source estimation from the 90–144 ms period yielded activity within LOC and V2 in both hemispheres across all conditions. The psilocybin-induced increase in the P1 component over O1/O2 electrode sites seen in the VEP waveform-analysis was localized most strongly in V2 and extended to LOC and V1 in the right hemisphere in the high-dose condition. The psilocybin induced increase in the source-density did neither correlate with visual (all P's>0.17) nor with auditory hallucinations (all P's>0.98).

N170

To quantify the modulation of the N170 component, area measurements over the 148–223 ms period were subjected to a $3 \times 2 \times 5 \times 2$ repeated measures ANOVA (using dose, hemiscalp, electrode, and stimulus as within factors). Psilocybin dose-dependently decreased the N170 amplitude ($F(2,32)=17.170$, $p<0.00001$, $\eta^2=0.52$) and bonferroni-corrected post-hoc analysis

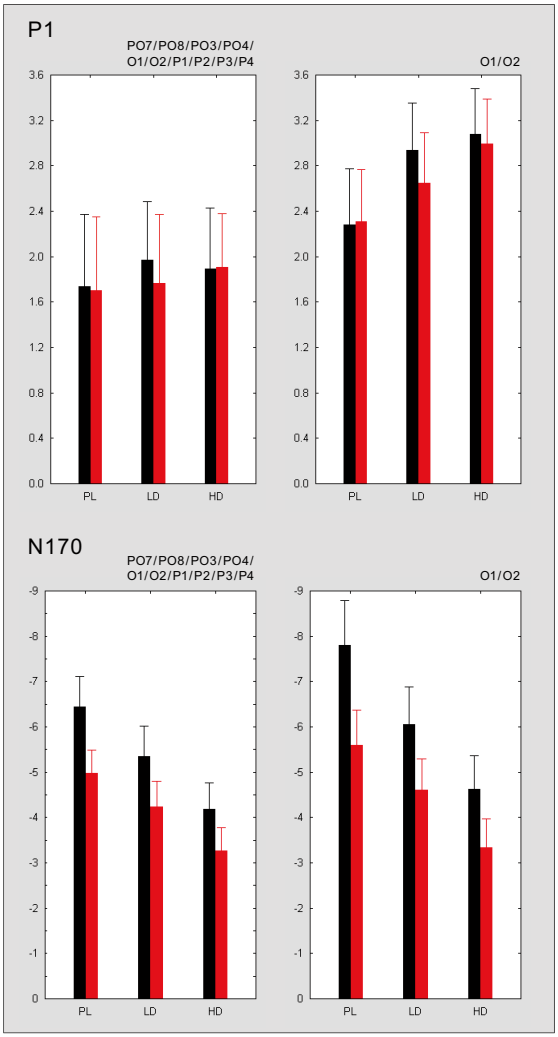

Figure 2
The bar graphs display mean areas of the P1 (top) and N170 (bottom) components measured from 10 parieto-occipital electrodes sites (left) and from occipital electrode sites O1/O2 (right) symmetrically localized over both hemiscalps (see Methods and Materials for details). Mean areas are displayed for Kanizsa-figures (black) and non-Kanizsa-figures (red) for all dose conditions (PL = placebo, LD = low-dose, HD = high-dose). Vertical bars denote standard deviations. The y axis presents amplitude in microvolts (μV).

revealed that the magnitude differences were significant between all dose conditions (Figure 2). The significant interaction between dose and hemiscalp ($F(2,32)=5.30$, $p<0.05$, $\eta^2=0.25$) and the visual inspection of the VEP indicated a stronger psilocybin-induced decrease over the right compared to the left hemiscalp. In accordance with numerous previous studies (20–25) a significant main effect of the stimulus condition was observed ($F(1,16)=35.863$, $p<0.0001$, $\eta^2=0.70$), with a greater magnitude in the Kanizsa- compared to the non-Kanizsa-condition. This magnitude difference between Kanizsa- and non-Kanizsa conditions dose-dependently decreased as revealed by the significant interaction between dose and condition ($F(2,32)=3.4485$, $p<0.05$, $\eta^2=0.18$).

The topographic pattern analysis of the collective data indicated that the effects of strength modulation in the electrical field were not associated with topographic modulations. This was subsequently confirmed by subjecting individual subject data to repeated measures ANOVA (all P's>0.25).

LORETA source localization over the N170 period (148–223 ms)

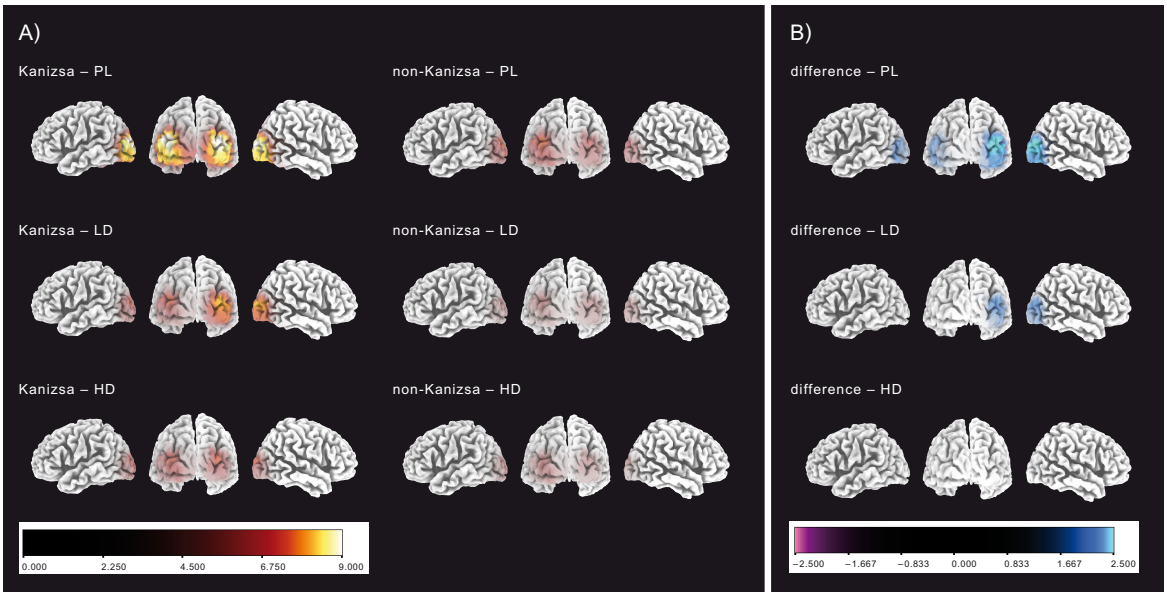

Figure 3
A) Group-averaged LORETA source estimations for each stimulus (Kanizsa, non-Kanizsa) and dose (PL = placebo, LD = low-dose, HD = high-dose) conditions over the N170 period (148–223 ms). B) Group-averaged differences of the source estimations between Kanizisa and non-Kanizsa condition.

The source estimation revealed activity within LOC and V2 in both hemispheres in all conditions (Figure 3). Current source density was stronger within right-lateralized LOC and V2 in the Kanizsa- compared to non-Kanizsa-condition. Psilocybin dose-dependently decreased the differential activation of the two stimulus conditions and reduced the current source density within LOC, V2 and fusiform gyrus in both stimulus conditions. The psilocybin-induced current source density reduction over right-lateralized LOC, V2 and posterior parietal areas correlated significantly with the increased intensity of visual hallucinations (Figure 4), while no correlation could be revealed with auditory hallucinations (all P's>0.64).

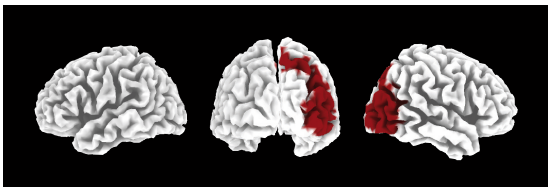

Figure 4
The voxel-wise correlation between visual hallucinations and placebo – psilocybin current source density difference revealed that psilocybin-induced decrease in current source density in right extrastriate areas and posterior parietal areas over the N170 period (148–223 ms) positively correlated with the intensity of visual hallucinations (significant areas $p<0.05$ are shown in red). 194 voxels reached 0.05 significance criterion with a mean r value of 0.57.

3.5 Discussion

The present investigation revealed three main findings. First, the data indicate that the mixed 5-HT2A/1A-receptor agonist psilocybin distinctively modulates the two early visual processing components. Specifically, while we found a strong dose-dependent decrease of the N170 component (148–223 ms post-stimulus) the earlier visual P1 component (90–144 ms post-stimulus) was slightly increased over occipital electrode sites. Second, the reduction of the N170 component was stronger for the Kanizsa-figure condition as compared to the non-Kanizsa condition. Third, during this time range the decrease in activation over right-lateralized extrastriate and posterior parietal cortex correlated with the reported intensity of visual hallucinations.

The time frame of the N170 component has been regarded as a critical period for object completion based on numerous findings of enhanced N170 amplitude and underlying LOC and V2 activation evoked by Kanizsa- compared to control figures (20–25). The preferential reduction of the N170 amplitude in Kanizsa compared to non-Kanizsa condition by psilocybin indicates a central role of the 5-HT2A/1A receptors in object-completion. Since two sub-processes of object completion, i.e. boundary completion (22) and region-based segmentation (25), have been

shown to underlay the enhanced N170 amplitude in the Kanizsa-condition, it would be interesting to further investigate which of these two sub-processes is modulated by signal transmission at 5-HT2A/1A receptors.

The finding that psilocybin slightly enhanced P1 amplitude may reflect a generalized effect of 5-HT2A/1A mediated increase in perceived brightness which is often reported after indolamine hallucinogen administration (40). This is supported by previous studies using comparable Kanizsa-figures showing the P1 component to be sensitive to stimulus brightness (41) as well as eccentricity (20) and symmetry (41).

Given that psilocybin strongly decreased the N170 amplitude in both the Kanizsa and the non-Kanizsa conditions, we suggest that it modulates additional processes beyond proper object completion. Disruption of these processes might play a role in visual hallucinations, since their reported intensity was significantly correlated with the 3-dimensional current source density reduction over right-lateralized LOC, V2 and posterior parietal areas during the time-frame of the N170 component. This localization is in agreement with previous imaging studies reporting decreased extrastriate activation in response to external visual stimuli in patients with visual hallucinations compared to patients without hallucinations (42–44). Furthermore, we found decreased activation specifically during the time-range of the N170 component. Decreased activation during this time range has been previously reported in studies investigating acoustic (45, 46) and visual hallucinations (23). We therefore suggest that decreased stimulus-induced activation in modality-specific cortical areas during the time range of the N1/N170 component may be a characteristic of acoustic as well as visual hallucinations. This relationship between the increased intensity of visual hallucinations and the decreased stimulus-evoked activation of extrastriate areas during the time-range of the N170 component could reflect a competition for neuronal resources in the processing of internally (hallucination) and externally (sensory-driven) generated information (46, 47). A comparable mechanism has previously been suggested to be relevant in the formation of acoustic hallucinations (48). Increased extrastriate activation which could interfere with the processing of external stimuli, has been observed previously during visual hallucinations in the absence of external stimulation in different psychiatric disorders (43, 49–51) as well as after psilocybin administration (29). In line with this interpretation we additionally found a correlation between reduced posterior parietal activation and hallucinatory severity. The posterior parietal cortex controls attention to visual stimuli by modulating visual cortex activity (52) during the time-range of the N170 component (53). The reduced posterior parietal activation might therefore reflect a psilocybin-induced failure to allocate attention and thus neuronal resources to external stimuli.

Importantly, we identified reduced extrastriate visual cortex activation during the time range of the N170 as a potential key component of 5-HT2A/1A agonist-induced visual hallucinations. Such a mechanism could also underlie the visual disturbances and hallucinations reported in

Parkinson and schizophrenia patients, since increased 5-HT2A receptor densities have been found in these conditions and associated with visual hallucinations (6, 8, 9). In support of this notion, Parkinson's patients with visual hallucinations showed more pronounced impairments in visual object recognition (54, 55) and more prominent reductions in extrastriate cortex activation to visual stimuli than patients without hallucinations (44). Moreover, a reduction of the N170 component has also been reported in schizophrenia patients and associated with visual hallucinations using Kanizsa-figures (23). These observations are in line with our finding of a correlation between reduced extrastriate activation during the time range of the N170 component and the intensity of visual hallucinations. It is noteworthy, however, that two other previous studies using Kanizsa-figures in schizophrenia reported either no reduction (24) or only a reduction at a trend level (56). The apparent discrepancy between these results and our findings may be due to the fact that only about 30% of schizophrenia patients typically report visual hallucinations (57) and many of the patients tested were medicated with atypical antipsychotics with 5-HT2A antagonistic activity. It might, therefore be possible that a disrupted 5-HT2A receptor system may be relevant only to a subgroup of schizophrenia patients. Given that we did not find a decrease of the P1 component after psilocybin administration and the robust reduction of the P1 component reported in schizophrenia (23, 24, 56, 58) was not associated with psychotic symptoms (58) suggests that the reduction of the P1 component in schizophrenia is not related to serotonergic alterations and may rather represent an endophenotype of the schizophrenia spectrum (58, 59).

Since psilocybin is a mixed 5-HT2A/1A agonist (60) resulting in downstream effects on the dopamine systems (61), the exact pharmacological mechanisms of the observed psilocybin effects require further investigation. However, converging lines of evidence indicate that psilocybin's psychotomimetic effects are mediated through the 5-HT2A receptor activation (10, 62). For example, behavioral effects of psilocybin are lacking in 5-HT2A receptor knockout mice (63) and in humans nearly all psychotomimetic effects including visual distortions and hallucinations can be blocked by the 5-HT2A antagonist ketanserin (64, 65), but not by blocking downstream dopaminergic effects with haloperidol (64). These findings, in combination with evidence regarding the importance of the 5-HT2A receptors in the pathophysiology of visual hallucinations (6–9), indicate that the reported effects of psilocybin are likely to be mediated by 5-HT2A receptor activation. However, given that 5-HT1A receptors additionally influence the psychotomimetic effects of indolamine hallucinogens (66) and 5-HT1A receptors are widespread in the visual cortex (1, 2), further studies are needed to exclude an additional contribution of 5-HT1A receptor on the spatiotemporal dynamics of visual object completion and hallucinations.

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3.7 Financial Disclosure

All authors report no financial interests or potential conflicts of interest with respect to this study.

3.8 References

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3.9 Supplemental Information

P300 Waveform analysis

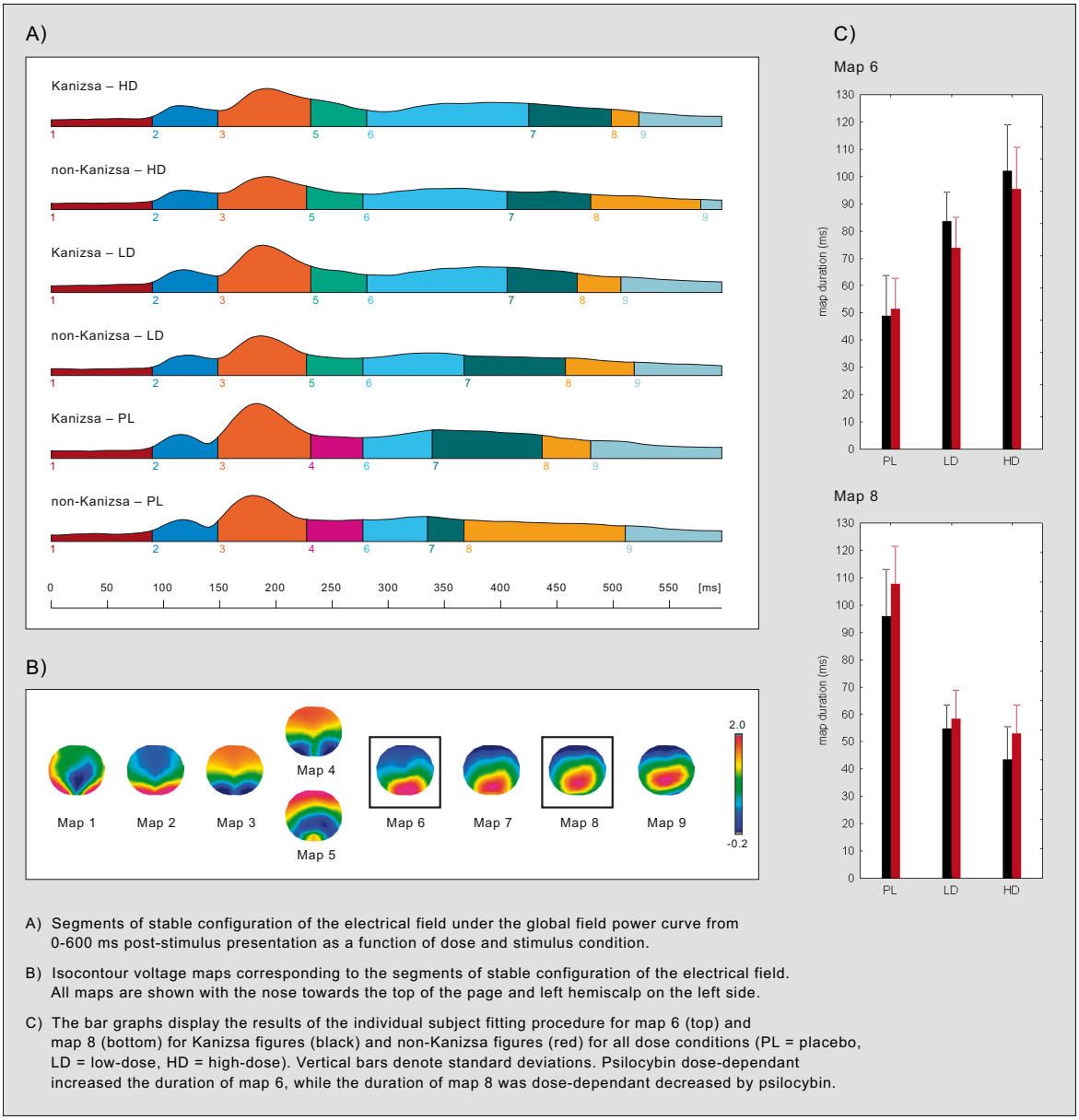
For the P300 component, mean amplitude measurements (versus the baseline) were conducted at standard P300 electrode sites Pz, Cz, Fz over the time range of 281–600 ms corresponding to the last 4 topographic maps. These values were subjected to a $3 \times 3 \times 2$ repeated measures ANOVA using dose (placebo, low-dose, high-dose), electrode (Pz, Cz, Fz), and stimulus (Kanizsa, Non-Kanizsa) as within factors.

ANOVA analysis yielded a main effect of electrode ($F(2,32) = 61.80$, $p < 0.00001$, $\eta^2 = 0.79$) with greatest magnitude over Pz followed by Cz and Fz electrode sites. Psilocybin dose-dependently decreased the P300 amplitude ($F(2,32) = 26.77$, $p < 0.00001$, $\eta^2 = 0.63$) and Bonferronicorrected post-hoc analysis indicated a significant magnitude difference between all dose conditions (Figure S2).

P300 Topographic analysis

The topographic pattern analysis of the group-averaged data indicated distinct durations of stable topographic distribution between different dose and stimulus conditions (Figure S1). To statistically confirm this finding, the duration of each map observed in the individual subject data was subjected to a repeated measure ANOVA. The significant interaction between dose and

map ($F(16,256)=5.25$, $p<0.00001$, $\eta^2=0.25$) indicated that the configurations of the electric field underlying the P300 component varies depending on the dose. Subsequent Bonferronicorrected post-hoc analysis revealed that map 6 starting 277 ms after stimulus presentation lasted significantly longer in the high-dose compared to placebo condition ($p<0.001$) while map 8 lasted longer in placebo compared to high-dose condition ($p<0.0001$) (Figure S1).

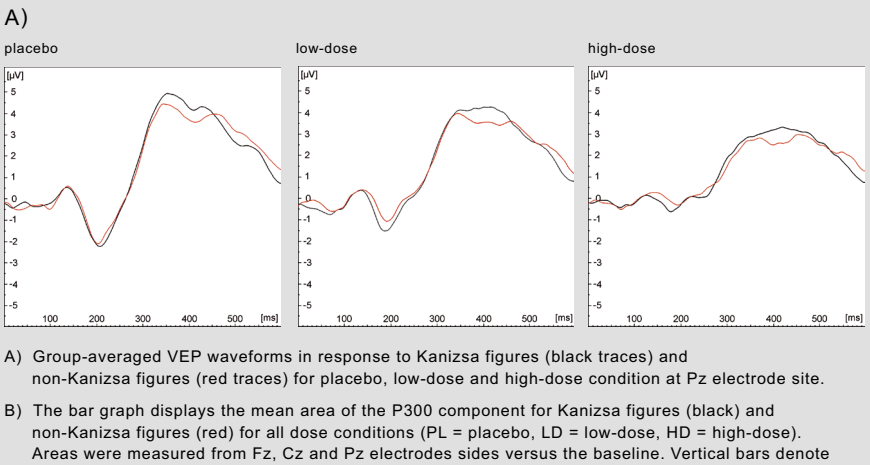


A) Segments of stable configuration of the electrical field under the global field power curve from 0-600 ms post-stimulus presentation as a function of dose and stimulus condition.

B) Isocontour voltage maps corresponding to the segments of stable configuration of the electrical field. All maps are shown with the nose towards the top of the page and left hemiscalp on the left side.

C) The bar graphs display the results of the individual subject fitting procedure for map 6 (top) and map 8 (bottom) for Kanizsa figures (black) and non-Kanizsa figures (red) for all dose conditions (PL = placebo, LD = low-dose, HD = high-dose). Vertical bars denote standard deviations. Psilocybin dose-dependant increased the duration of map 6, while the duration of map 8 was dose-dependant decreased by psilocybin.

Figure S1



A) Group-averaged VEP waveforms in response to Kanizsa figures (black traces) and non-Kanizsa figures (red traces) for placebo, low-dose and high-dose condition at Pz electrode site.

B) The bar graph displays the mean area of the P300 component for Kanizsa figures (black) and non-Kanizsa figures (red) for all dose conditions (PL = placebo, LD = low-dose, HD = high-dose). Areas were measured from Fz, Cz and Pz electrodes sides versus the baseline. Vertical bars denote standard deviations.

Figure S2

4

Psilocybin-induced effects on alpha oscillations, visual-evoked potentials and visual hallucinations depends on 5-HT2A receptor activation

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Personal contribution

M. K. conceived and designed the study, developed the task, and gathered and analyzed all behavioral and EEG data, interpreted the data and wrote the paper. F. X. V., A. S. and L. J. helped to design the study, gather data, interpret the data and/or revise the first draft of the paper.

4.1 Abstract

Visual illusion and hallucinations are a hallmark of serotonergic hallucinogen-induced states of consciousness. Although the serotonergic hallucinogen psilocybin displays high affinity for various serotonin (5-HT) subreceptors, recent evidence converge on the idea that 5-HT2A receptor activation may lead to increased cortical excitability and altered visual evoked cortical responses that underlay psilocybin-induced visual hallucinations. Here we assessed in healthy human subjects the effect of psilocybin (215 µg/kg vs. placebo) on the alpha oscillations that regulates cortical excitation and on the early visual-evoked potentials P1 and N170. To disentangle the specific contribution of 5-HT2A receptors, subjects were pretreated with the preferential 5-HT2A receptor antagonist ketanserin (50 mg vs. placebo). We found that psilocybin strongly decreased prestimulus parieto-occipital alpha power and blocked subsequent stimulus-induced alpha desynchronization, two effects that were reversed by ketanserin. Furthermore, the medial P1 visual-evoked potential was selectively increased by psilocybin and selectively decreased by ketanserin. Finally, psilocybin strongly decreased the N170 potential associated with the formation of subjective perceptual alterations, both of which were blocked by the 5-HT2A antagonist ketanserin. These findings suggest that 5-HT2A receptor activation mediates the psilocybin-induced subjective perceptual alteration and may induce a processing mode, in which stimulus-driven cortical excitation is overwhelmed by spontaneous neuronal excitation. The reduction the N170 visual-evoked potential might be a possible key mechanism of 5-HT2A receptor–mediated subjective perceptual alteration, which may be implicated not only in psilocybin-induced states but also in psychiatric disorders.

4.2 Introduction

Recent evidence from molecular, pharmacological and neuroimaging studies suggests a crucial role for serotonin 2A (5-HT2A) receptors in visual processing and the pathogenesis of visual hallucinations. Specifically, 5-HT2A receptors are highly expressed in the visual cortex (Gerstl et al., 2008; Watakabe et al., 2009; Moreau et al., 2010) and alterations in the their cortical density in Parkinson's disease (Ballanger et al., 2010; Huot et al., 2010) and schizophrenia (González-Maeso et al., 2008) are associated with the appearance of visual hallucinations. Furthermore, 5-HT2A receptors activation predominantly mediates the visual hallucinations induced by serotonergic hallucinogens such as psilocybin and LSD (Vollenweider et al., 1998; Nichols, 2004; Vollenweider and Kometer, 2010), whereas the 5-HT2A receptor inverse agonist pimavanserin is an effective treatment for visual hallucinations in Parkinson's disease (Meltzer et al., 2010). Despite the increasingly recognized significance of 5-HT2A receptors in visual perception, the effect of 5-HT2A

receptor activation by psilocybin on the neurophysiological mechanisms of visual processing and hallucinations remain unknown. Therefore, we assessed the modulation of the prestimulus state of the parieto-occipital network and the subsequent stimulus-induced activity by 5-HT2A receptor activation and evaluated the relationship of this modulation to the formation of visual perceptual alterations, including visual hallucinations.

The activation of 5-HT2A receptors increases the excitability of the visual cortex in animals in the absence of externally presented visual stimuli (Moreau et al., 2010). Computational models suggest that an increase in the excitability state of the visual cortex may destabilize spontaneous network activity, which produces elementary visual hallucinations (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012). Parieto-occipital alpha oscillations are crucial for the modulation of visual network excitability, which strongly influence visual perception (Thut et al., 2006; Romei et al., 2008a; Jensen and Mazaheri, 2010; Klimesch, 2011; Mathewson et al., 2011) and visual-evoked potentials (Gruber et al., 2005; Klimesch, 2011; Rajagovindan and Ding, 2011). Therefore, 5-HT2A receptor activation might modulate alpha power, which could lead to an altered excitability that promotes the formation of visual hallucinations.

In addition, 5-HT2A receptors activation may modulate the visual cortex response to external stimuli that are indexed by visual-evoked potentials, because the bioactive metabolite of psilocybin unselectively activates the 5-HT2A receptor (Blair et al., 2000; Nichols, 2004) and increases the early P1 visual-evoked potentials throughout medial occipital regions (Kometer et al., 2011). In addition, psilocybin decreases the N170 potential associated with the intensity of psilocybin-induced visual hallucinations (Kometer et al., 2011). The 5-HT2A receptors likely mediate this psilocybin-induced decrease in the N170 potential because 5-HT2A receptor activation predominantly mediates psilocybin-induced visual hallucinations (Vollenweider et al., 1998; Vollenweider and Kometer, 2010). However, psilocybin also activates 5-HT1A, 2C receptors (Nichols, 2004; Vollenweider and Kometer, 2010), and at least the 5-HT1A receptor is also expressed with a low density in the visual cortex (Dyck and Cynader, 1993; Gerstl et al., 2008; Watakabe et al., 2009). Therefore the question about the specific effect of 5-HT2A receptor activation on visual-evoked potentials and the P1 potential in particular, remains unknown.

4.3 Methods

4.3.1 Subjects

Seventeen right-handed subjects (11 males, 6 females, mean age of 26.0 ± 4.36 years) were enrolled. All subjects were healthy on physical examination, which included detailed blood analyses and electrocardiography. The Mini-International Neuropsychiatric Interview, MINI-SCID

(Sheehan et al., 1998), the DIA-X diagnostic expert system (Wittchen and Pfister, 1997), and the Hopkins Symptom Checklist SCL-90-R (Derogatis, 1994) were used to exclude subjects with present or antecedent psychiatric disorders or a history of major psychiatric disorders in first-degree relatives. A urine drug screen and a self-report drug use questionnaire verified the absence of substance dependence.

Subjects received a written and oral description of the study procedures and the effects and possible risks of psilocybin administration. Subjects provided written informed consent prior to study participation. One of the 17 subjects was excluded due to dizziness after the combined administration of psilocybin and ketanserin. The data of another subject were excluded from analyses because the majority of the trials were contaminated by artifacts. A total of 15 subjects were included in the statistical analysis.

4.3.2 Substance and Dosing

A double-blind, placebo-controlled, within-subject, randomized design was used. Subjects received on four experimental days that were separated by at least two weeks four different drug combinations: placebo and ketanserin (50 mg) (pretreatment) followed by placebo and psilocybin (215 µg/kg) (treatment) after one hour. These specific doses were chosen, because they have been shown to induce and block the associated changes in conscious states (Carter et al., 2005). The Kanizsa experiment began 90 min after treatment during the plateau of the peak subjective psilocybin effects (Studerus et al., 2011). Self-report questionnaires were completed 360 min posttreatment to retrospectively rate the subjective experience following drug intake.

The use of psilocybin in humans was authorized by the Swiss Federal Office of Public Health, Department of Pharmacology and Narcotics (DPN), Bern, Switzerland. The study was approved by the ethics committee of the University Hospital of Psychiatry, Zurich.

4.3.3 Self-report questionnaires

The Five Dimensions of Altered States of Consciousness (5D-ASC) questionnaire (Dittrich) was used to quantify the subjective psychological effects of drug administration, with a primary focus on visual alterations and hallucinations. The 5D-ASC is a visual analogue scale of 94 items that measure etiology independent alterations in consciousness, including changes in mood, perception, cognition, and experience of the self and the environment. The Visionary Restructuralization factor of the 5D-ASC, which measures visual illusions and elementary and complex hallucinations, was the primary interest of the current study. We also used the finer subdivision of the 5D-APZ in 11 subscales for exploratory analysis (Studerus et al., 2010).

4.3.4 Stimulus and procedure

Subjects remained fixated on a central fixation cross during Kanizsa and control figure presentations. All stimuli included three “pacman” figures, i. e., a black circle with a 60° section removed. The removed sectors were either aligned to induce the perception of an illusory triangle (“Kanizsa” condition) or rotated 180°, which no longer induced the illusory triangle perception (“non-Kanizsa” condition). The visual angle of the stimuli was 5.4° instead of the 3.7° used in our previous Kanizsa study (Kometer et al., 2011), because increased eccentricity induces higher P1 amplitudes (Murray et al., 2002; Busch et al., 2004). The stimuli were presented in four orientations of equal number, rotated 0°, 90°, 180°, and 270°, to reduce habituation. In total, 88 Kanizsa figures and 88 non-Kanizsa figures were presented in a randomized order with a 3 sec stimulus onset asynchrony. Participants responded with a button press as quickly as possible when they perceived an illusory triangle on each trial. Stimuli remained on the monitor for 300 msec after a button press or for a maximum of 2000 msec.

4.3.5 EEG recording

Continuous EEG was acquired from 64 Ag-AgCl electrodes using the BioSemi ActiveTow electrode system. Additional electrodes were attached to the outer canthus of each eye and infraorbitally and supraorbitally to the left eye to record the horizontal and vertical electrooculograms (EOGs), respectively. Electrophysiological signals were band-pass filtered online between 0.01 and 67 Hz and digitized with a sampling rate of 512 Hz.

4.3.6 EEG analysis

Preprocessing

The EEG data were recalculated offline against the common average reference, and bad channels (< 2%) were interpolated using spherical splines (Perrin et al., 1989). EEG data were epoched from 800 ms before to 600 ms after stimulus onset. An automatic artifact rejection excluded epochs in which voltage values of the raw unfiltered data exceeded ± 120 µV in four or more electrodes to avoid eye movements, periods of high muscle activity and other noise transients. The remaining epochs were screened manually to reject epochs with residual eye movement artifacts.

Time-frequency analysis

Signals x(t) from each trial were convolved with a family of Morlet wavelets, $w(t, f_o) = A \exp(-t^2 / 2 \sigma_t^2) \exp(2i\pi f_o t)$, where f_o is the central frequency, and i is the imaginary part, to calculate phase and power at 1-Hz frequency steps between 4 and 100 Hz. Wavelets were normalized using the factor

$A(w) = (\sigma_t \sqrt{\pi})^{-1/2}$. The family ratio, $m = f_o / \sigma_f = 5$, was used, where σf is the width of the Gaussian shape in the frequency domain. This ratio was used to optimize the trade-off between the temporal and frequency resolutions of the wavelet convolution.

The power for each trial was computed as the sum of the squares of the real and the imaginary Morlet wavelet components, which was subsequently averaged over single trials separately for all conditions. These power values were baseline corrected by subtracting the mean power over the -200 to 0 ms prestimulus interval to quantify the stimulus-induced power.

The extent of normalized phase variability across trials for each condition was quantified using the phase-locking value PLV (also called intertribal coherence (ITC) or phase-locking factor) at each time point, t, and frequency, f_o. This procedure yields a PLV measure that ranges from 0 to 1. A value of 0 indicates completely randomized phases across different trials at a specific time point, t, and 1 indicates a consistent phase across trials.

Event-related potential (ERP) analysis

Individual ERPs were computed as the average across all trials per condition after the band-pass filtering of the preprocessed data (see above) at 0.5–40 Hz. The P1 and N170 amplitudes were quantified against the 200 ms baseline as the mean amplitude during a 40 ms time frame that was centered on the peak maximum time point, which resulted in a time frame from 80–120 ms for the P1 and 150–190 ms for the N170.

Statistical analysis

Three parieto-occipital regions of interest (ROIs) were selected for the statistical analysis of ERPs, alpha power and phase, including the following electrodes: parietal left (P3, P5, P7, PO3, PO7), parietal medial (POz, Oz, O1, O2, Iz) and parietal right (P4, P6, P8, PO4, PO8). These ROIs have previously been used to quantify alpha power and phase values (Zanto et al., 2011) and covered the maximal P1 and N170 amplitudes in the current study.

Only the time frame between -600 ms and 400 ms was considered in the analyses of power and phase values to ensure that edge effects did not contaminate the statistical analyses (Cohen et al., 2007). Prestimulus alpha (8–12 Hz) power was collapsed over the -600 to 0 ms time frame. Poststimulus alpha power was collapsed into two time frames (0–200 ms and 200–400 ms) because visual inspection of our data indicated a stimulus-induced increase during the first time frame (0–200 ms) and a strong alpha desynchronization during the second time frame (200–400 ms) (Figure 3).

All dependent variables were subjected to repeated-measures ANOVA (specific factors are defined in the results section), and Greenhouse-Geisser correction was applied. Bonferroni-corrected post-hoc comparisons were performed based on significant main effects or interactions. Pearson's product moment correlations were conducted to assess several hypothesis-driven

relationships between physiological parameters and self-reported visual perceptual alterations. First, we replicate (Kometer et al., 2011) and specify the relationship between the psilocybin-induced decrease of the N170 potential and perceptual alterations. Second, we tested whether increased excitability that is indexed with decreased alpha-oscillations (Thut et al., 2006; Romei et al., 2008a; Jensen and Mazaheri, 2010; Klimesch, 2011; Mathewson et al., 2011) results in elementary hallucinations (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012) by correlating alpha power with the elementary hallucination subscale of the 5D-APZ (Studerus et al., 2010). Finally, psilocybin-induced changes in prestimulus alpha power were correlated with the psilocybin-induced changes in the P1 potential, because the prestimulus alpha power has previously been closely associated with the P1 potential (Klimesch, 2011; Rajagovindan and Ding, 2011).

4.4 Results

4.4.1 Behavioral data

Psychometrics

Repeated-measures ANOVA on the 3 primary dimensions of the 5D-ASC rating scale using pretreatment, treatment and dimensions as within factors revealed a main effect of treatment ($F(1,14)=75.85$, $p<0.00000050$) and a treatmen×pretreatment interaction ($F(1,14)=85.05$, $p<0.00000025$). Post-hoc analyses of this interaction indicated that treatment with psilocybin increased 5D-ASC scores after placebo pretreatment ($p<0.000000011$), but not ketanserin pretreatment ($p=1$). The triple interaction between pretreatment × treatment × factor ($F(2,28)=30.62$, $p<0.000000090$) demonstrated a similar relationship for the Visionary Restructuralization subdimension; the strong psilocybin-induced increase ($p<0.000036$) was absent after ketanserin pretreatment ($p=1$). The scores of the recently formed 11 subscales (see Methods) were submitted to a separate repeated-measures ANOVA. The triple interaction between treatment × pretreatment × factor ($F(10,140)=9.44$, $p<0.00000000000070$) indicated that psilocybin robustly induced several perceptual alterations after placebo pretreatment, including complex hallucinations ($p<0.0000001$), elementary hallucinations ($p<0.0000001$), audio-visual synethesiae ($p<0.000043$) and changed meaning of percepts ($p<0.0000001$). However, no subscales were altered after ketanserin pretreatment (all p values = 1).

Reaction times (RT) and Error rates

RT for correct responses were not significantly altered by psilocybin ($F(1,14)=2.163$, $p=0.16$) or ketanserin ($F(1,14)=0.192$, $p=0.090$). Error rates remained low in all drug conditions, and

neither treatment ($F(1,14)=0.21$, $p=0.65$) nor pretreatment ($F(1,14)=3.73$, $p=0.074$) generally modulated error rates. However, the interaction between treatment and stumulus ($F(1,14)=5.124$, $p<0.041$) indicated that psilocybin increased error rates for Kanizsa stimuli ($p<0.039$) but not the non-Kanizsa stumuli ($p=1$).

4.4.2 Event-related potential analyses

P1

A repeated-measures ANOVA on P1 amplitudes (using pretreatment, treatment, stimulus and ROI as within factors) revealed a significant interaction between treatment and ROI ($F(2,28)=8.153$, $p<0.0017$) and pretreatment and ROI ($F(2,28)=19.879$, $p<0.0000043$). Post-hoc analyses of these interactions indicated that psilocybin selectively increased the P1 amplitudes over the medial ($p<0.045$) but not the lateral parieto-occipital ROIs. In contrast, the P1 amplitudes over the medial parieto-occipital ROI was selectively decreased by ketanserin ($p<0.000003$) (Figure 1).

N170

A repeated-measures ANOVA on N170 amplitudes (using pretreatment, treatment, stimulus and ROI as within factors) revealed a significant main effect of treatment ($F(1,14)=5.336$, $p<0.037$), which replicated a previous study of psilocybin-induced decrease in the N170 amplitude (Kometer et al., 2011). In addition, the significant interaction between treatment and

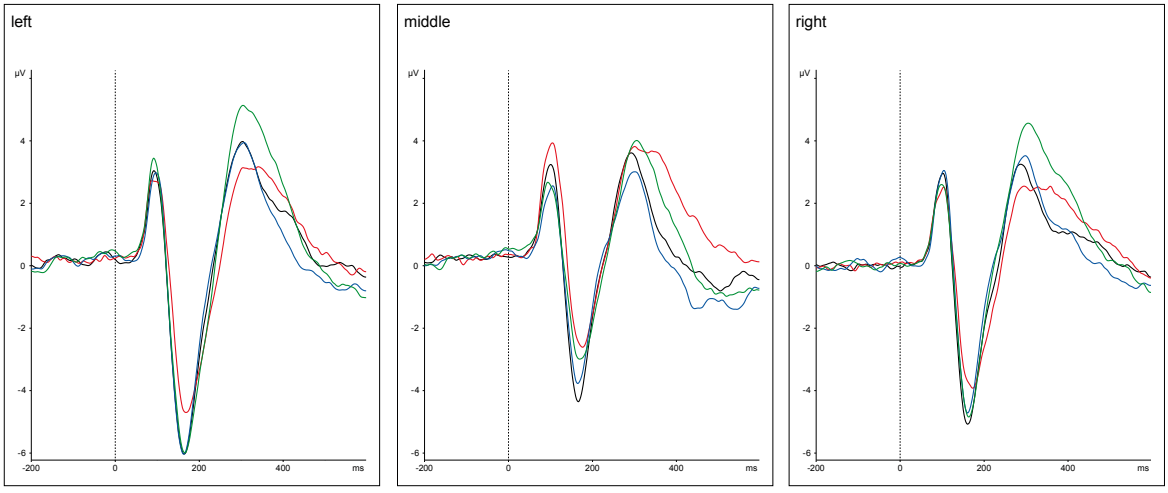

Figure 1: Effect of psilocybin and ketanserin on the group-averaged event-related potential waveforms for the three parieto-occipital ROIs. Placebo + Placebo (black), Placebo + Psilocybin (red), Ketanserin + Placebo (blue), Ketanserin + Psilocybin (green).

pretreatment ($F(1,14)=7.548$, $p<0.016$) and the subsequent post-hoc analyses indicated that psilocybin treatment decreased the N170 component compared to placebo only after placebo pretreatment ($p<0.006$) but not ketanserin pretreatment ($p=1$) (Figure 1). Correlational analysis revealed that this psilocybin-induced N170 decrease correlated with the psilocybin-induced increase in Visionary Restructuralization ($r=0.7253$, $p<0.0023$), and several subscales (complex imagery $r=0.6100$, $p<0.0158$; elementary imagery $r=0.4857$, $p<0.0665$; Audio-visual synesthesiae $r=0.5378$, $p<0.0388$) (Figure 2).

A significant main effect of stimulus was revealed ($F(1,14)=113.107$, $p<0.000000044$) because the N170 amplitude was higher for the Kanizsa stimuli than for the non-Kanizsa stimuli. However, the interaction of stimulus and treatment did not reach significance ($F(1,14)=1.86$, $p=0.19$) in contrast to our previous study (Kometer et al., 2011). We suggest that although the slightly higher stimulus size may also have contributed to the lack of effect in the current study, the more complex pharmacological statistical design, which added additional variance, was probably the primary contributor. To confirm this hypothesis, we calculated an additional ANOVA that included only the placebo+placebo and the placebo+psilocybin conditions. This ANOVA yielded a significant interaction between treatment and stimulus ($F(1,14)=4.96$, $p<0.043$), indicating a stronger psilocybin-induced decrease in the N170 potential in the Kanizsa ($p<0.00000015$) compared to that in the non-Kanizsa condition ($p<0.000089$).

4.4.3 Time-frequency analyses

Prestimulus alpha power

The alpha power (8–12 Hz) during the prestimulus time frame (-600 to 0 ms) was subjected to repeated-measures ANOVA (using pretreatment, treatment, stimulus and ROI as within factors). A main effect of ROI ($F(2,28)=4.130$, $p<0.027$) indicated that the alpha power was most pronounced over the right parieto-occipital region. Psilocybin strongly decreased the prestimulus

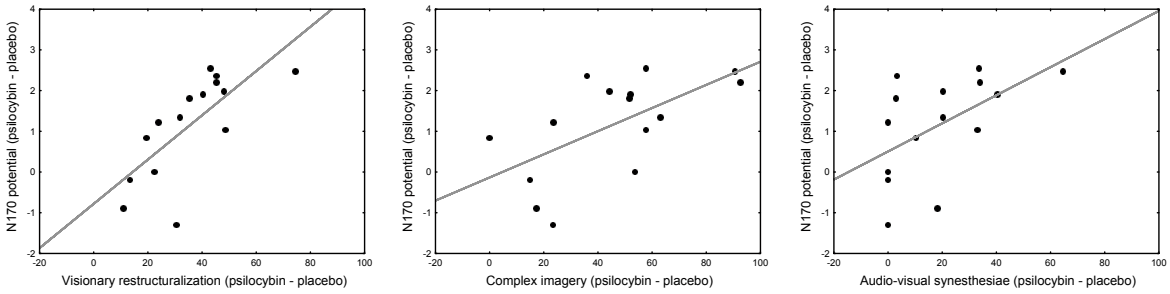

Figure 2: Correlation analysis between the psilocybin-induced reduction of the N170 and the psilocybin-induced self-reported perceptual visual alterations.

alpha power ($F(1,14)=13.777$, $p<0.0024$). This decrease depended on the pretreatment condition ($F(1,14)=5.953$, $p<0.029$) because the psilocybin-induced decrease in the alpha power was significant after pretreatment with the placebo ($p=0.00064$) but not ketanserin ($p=0.498$) (Figure 3). Correlational analysis revealed that the psilocybin-induced decrease in alpha power correlated significantly with the psilocybin-induced increase in the medial P1 potential ($r=-0.6409$, $p<0.011$).

Poststimulus Alpha Power

Repeated ANOVA on the poststimulus alpha power (using the pretreatment, treatment, stimulus, time and ROI as within factors) revealed a main effect of time ($F(1,14)=32.804$, $p<0.000052$), indicating a decrease in alpha power from baseline level (i.e. indicating stimulus-induced alpha

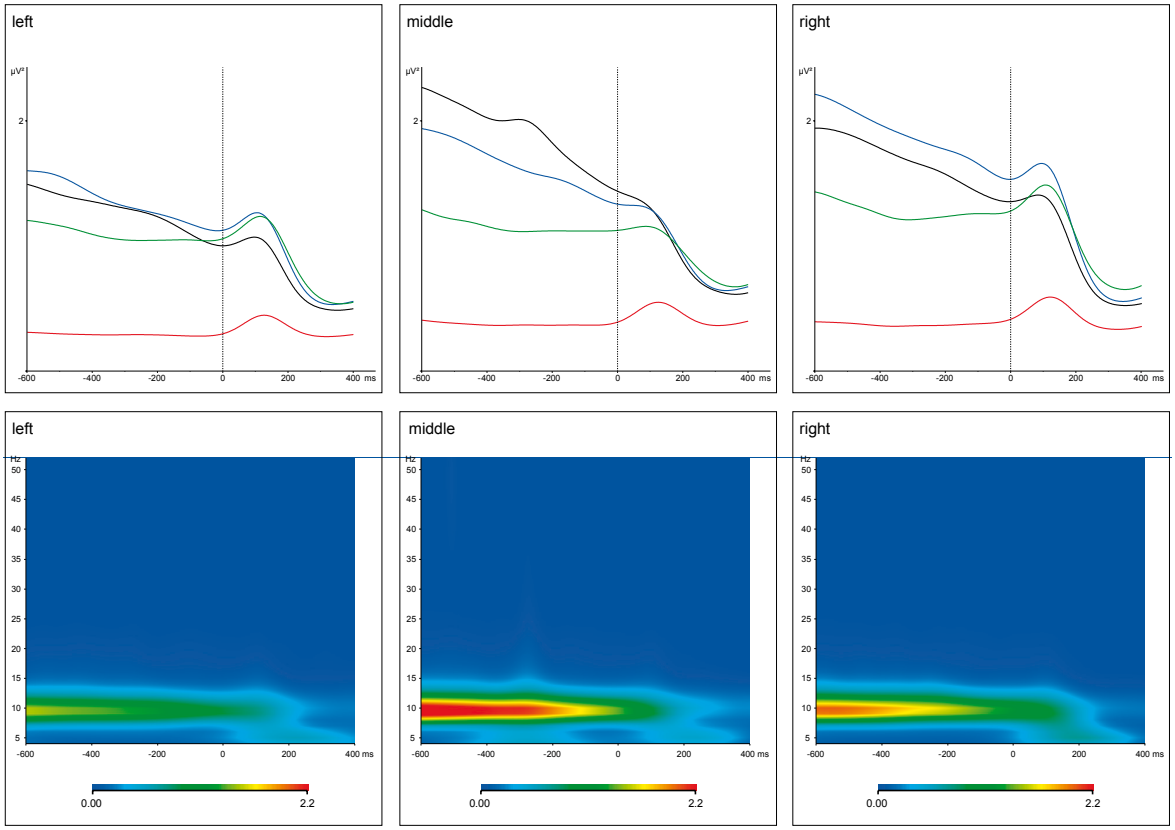

Figure 3: Effects of psilocybin and ketanserin on alpha power over the three parieto-occipital ROIs. Top: Time course for alpha power (8–12 Hz) as a function of Placebo + Placebo (black), Placebo + Psilocybin (red), Ketanserin + Placebo (blue), Ketanserin + Psilocybin (green). Bottom: Time course for the difference between Psilo-Pla for all frequences (4–52 Hz).

desynchronization), during the 200–400 ms time frame (Figure 3). The significant interaction between time × treatment ($F(1,14)=16.579$, $p<0.0011$) revealed that psilocybin reduced alpha desynchronization compared to placebo particularly during the 200–400 ms time frame ($p<0.0000003$). The 3-way interaction between treatment × pretreatment × time ($F(1,14)=7.237$, $p<0.018$) further indicated that this psilocybin-induced reduction of alpha desynchronization during the 200–400 ms time frame was reversed by ketanserin pretreatment, because alpha desychnroisation was significantly higher in the ketanserin + psilocybin condition than the placebo+psilocybin condition ($p<0.000057$).

Phase-locking Index (PLI)

Repeated-measures ANOVA (using the pretreatment, treatment, time, stimulus and ROI as within factors) on the PLI revealed a main effect of time ($F(1,14)=30.739$, $p<0.00008$), indicating particularly high PLI values during the 0–200 ms time frame. The significant interaction between pretreatment and time ($F(1,14)=37.599$, $p<0.000027$) indicated that ketanserin pretreatment decreased PLI during the 0–200 ms time frame ($p<0.000057$) but not during the 200–400 ms time frame ($p=0.439$). This decrease was most pronounced over the medial parieto-occipital ROI ($p<0.00000000017$) followed by the left ($p<0.00040$) and right parieto-occipital ROIs ($p<0.0025$) (pretreatment × time × ROI: ($F(2,28)=5.556$, $p<0.0093$) (Figure 4).

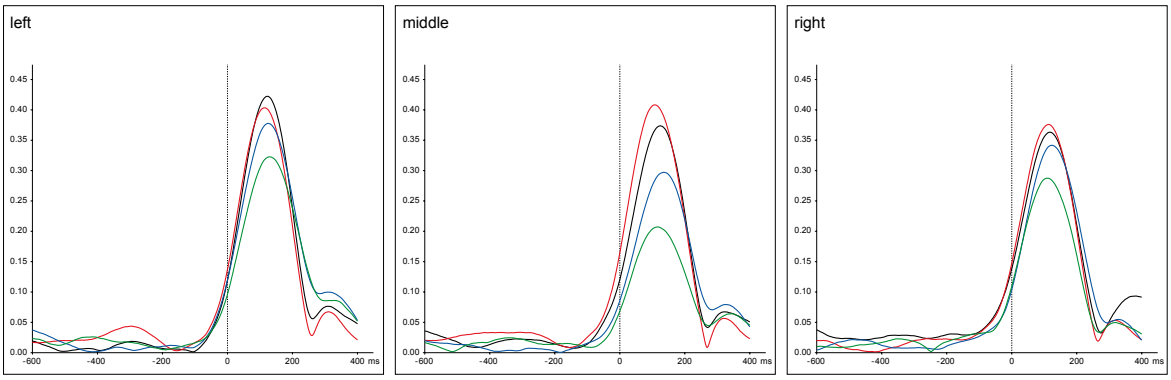

Figure 4: Effects of psilocybin and ketanserin on the Phase-locking-index for the three parieto-occipital ROIs. Placebo + Placebo (black), Placebo + Psilocybin (red), Ketanserin + Placebo (blue), Ketanserin + Psilocybin (green).

4.5 Discussion

The current study revealed that psilocybin strongly decreased prestimulus alpha power, but it blocked the stimulus-induced reduction in alpha power (i.e., it blocked alpha desynchronization). Moreover, psilocybin decreased the N170 visual-evoked potential. These psilocybin-induced effects on alpha oscillation and N170 visual-evoked potentials were normalized by the 5-HT2A antagonist ketanserin, indicating that 5-HT2A receptor activation is crucial in mediating these phenomenons.

Alpha oscillations (8–12 Hz) have been identified as a major neural mechanism that regulates by inhibition the excitability level of cortical sensory networks (Thut et al., 2006; Romei et al., 2008a; Jensen and Mazaheri, 2010; Klimesch, 2011; Mathewson et al., 2011). A high parieto-occipital alpha power level was observed under placebo conditions during the prestimulus time range, which suggests a high level of inhibition that reduces the excitability of the visual network in the absence of task-relevant visual input (Klimesch, 2011; Palva and Palva, 2011). This high level of prestimulus alpha power was strongly attenuated by psilocybin and reversed by ketanserin pretreatment, suggesting that the activation of 5-HT2A receptors increases the excitability of the visual network in the absence the absence of externally presented stimuli. By contrast, the stimulus-induced decrease in alpha power (i.e., "alpha-desynchronization") at 200–400 ms poststimulus was blocked by psilocybin and again reversed by ketanserin pretreatment. This finding suggests, that 5-HT2A receptor stimulation disrupts stimulus-driven excitability, which is indexed by the stimulus-induced alpha-desynchronization (Klimesch et al., 1994; Hanslmayr et al., 2009; Klimesch, 2011).

This opposite effect of 5-HT2A receptor activation on the excitability of the visual network during the presence or absence of externally presented stimuli might reflect a bias away from external stimulus-driven towards an internal-driven information processing, which may underlie the formation of visual hallucinations (Allen et al., 2008; Kometer et al., 2011; Butler et al., 2012). For instance, several computational models postulate that an increase in the excitability of the visual network in the absence of visual input destabilizes spontaneous neuronal activity, which results in the formation of elementary visual hallucinations (Ermentrout and Cowan, 1979; Bressloff et al., 2002; Gutkin et al., 2003; Butler et al., 2012) that resemble the visual hallucinations produced by classic hallucinogens (Klüver, 1966; Siegel et al., 1975). In addition, an increased stimulus-independent excitability that is associated with low alpha power has been implicated in TMS-induced phosphenes because the likelihood of experiencing these percepts is higher during low compared high alpha powers (Romei et al., 2008b). Psilocybin strongly increased the excitability in the absence of externally presented stimuli by decreasing alpha power and robustly induced elementary hallucinations in almost all of the subjects, which suggests that these alpha

effects may be implicated in the formation of visual hallucinations. However, the correlation between the psilocybin-induced decrease in alpha power and the subject-reported intensity of visual hallucinations did not reach statistical significance, indicating that the alpha power decrease may not be sufficient to generate a subjectively experienced visual hallucination.

The strong effect of 5-HT2A receptor activation on alpha power is consistent with the known anatomical and functional properties of 5-HT2A receptors in the visual cortex of animals. The 5-HT2A receptors in the visual cortex are primarily expressed in layers 4–6 (Watakabe et al., 2009; Moreau et al., 2010), which are crucially implicated in the generation of alpha rhythms (Steriade et al., 1990; Silva et al., 1991; Jones et al., 2000; Pinto et al., 2003; Bollimunta et al., 2008; Sun and Dan, 2009; Bollimunta et al., 2011; Buffalo et al., 2011). Furthermore, activation of 5-HT2A receptors in the visual cortex alters the excitatory-inhibitory balance towards excitation of neurons in layer V (Moreau et al., 2010). Excitatory synaptic inputs in layer V modulate alpha oscillations (Jones et al., 2000; Karameh et al., 2006; Sun and Dan, 2009), which suggests that 5-HT2A receptor-induced excitatory effects are closely associated with alpha oscillations. Finally, assuming that the presentation of external stimuli predominantly increases the firing rate of visual neurons from the prestimulus level (Quiroga et al., 2005; Montemurro et al., 2008), the opposite effect of 5-HT2A receptor stimulation during the present and absence of sensory stimuli in this study is consistent with the suppressive effect of 5-HT2A receptor activation on visual neurons with high firing rates, and the facilitatory effect on neurons with low firing rate (Watakabe et al., 2009).

Serotonin 2A receptors further strongly modulated the visual cortex response that is indexed by the visual-evoked P1 and N170 potentials. Specifically, psilocybin increased the medial P1 potential, and the preferential 5-HT2A antagonist ketanserin decreased the P1 potential over the same electrode sites. These results suggest an opposing influence of 5-HT2A agonism and antagonism on P1 potentials. Furthermore, these opposing effects seems to be either associated with alpha power or phase locking, which corresponds with the findings that the P1 potential is related to alpha oscillations (Gruber et al., 2005; Sauseng et al., 2005; Fellinger et al., 2011; Klimesch, 2011; Rajagovindan and Ding, 2011). Specifically, the individual decrease in prestimulus alpha power by psilocybin was significantly correlated with the psilocybin-induced increase in the P1 potential. Assuming that the initial visual gain is modulated by the prestimulus alpha power (Rajagovindan and Ding, 2011) and the psilocybin-induced increase in medial P1 potential reflects increased activity in early visual structures (Kometer et al., 2011), the psilocybin-induced increase in prestimulus excitability may have amplified the initial visual gain in early visual areas. In contrast, the decrease in the medial P1 after the administration of the 5-HT2A antagonist ketanserin was associated with a concomitant decrease in alpha phases locking, which was most pronounced over the medial parieto-occipital ROI. This result supports the notion that PLI and the P1 potential

are closely associated (Gruber et al., 2005; Fellinger et al., 2011) and that the attenuation of P1 potential may be driven by a 5-HT2A receptor antagonism-induced disruption of alpha phase resetting.

Furthermore, the N170 potential was decreased by psilocybin and associated with perceptual alterations, including visual hallucinations and audiovisual synethesia. Both the N170 potential and the perceptual alterations were blocked by ketanserin. This result not only supports that 5-HT2A rather than 5-HT1A receptor stimulation is the key mechanism of psilocybin-induced visual hallucinations (Vollenweider et al., 1998; Kometer et al., 2011) and audiovisual synesthesia, but further suggests that the decrease in the N170 potential is a crucial mechanism that underlies these 5-HT2A receptor-mediated subjective visual perceptual alterations. This mechanism might also be implicated in the pathophysiology of visual hallucinations in a subgroup of schizophrenic patients that experience visual hallucinations because this subgroup has increased cortical expression of 5-HT2A receptors (González-Maeso et al., 2008) and a more pronounced attenuation of the N170 potential to visual stimuli (Spencer et al., 2004).

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5

General Discussion

5.1 The effects of psilocybin on emotional and visual processing

5.1.1 Emotional processing

We found that psilocybin biases emotional processing towards positive relative to negative information across different psychological domains. Specifically, psilocybin predominantly induced positive mood states, which is evident by the marked increase in the scores of the "positive affect" subscale of the clinically relevant PANAS questionnaire. The strongly significant increase in the scores of the "blissful" subscale of the 5D-ASC questionnaire further indicate that these positive mood states are dominated by feelings of peace, love and happiness. In contrast, negative mood states were not provoked by psilocybin, as none of the scores of the "negative affect" subscale of the PANAS, "anxiety" subscale of the 5D-ASC or State-Anxiety of the State-Trait Anxiety Inventory were significantly altered from those of the placebo.

Similar to these alterations in the subjective state, a positive emotional bias was revealed in our study at the behavioural level by the psilocybin-induced bias towards the recognition of positive compared to negative emotional states of human eye regions, a processing mode that may cause increased trust in other people (Bedi et al., 2010). Furthermore, we found that psilocybin enhance the response bias towards positive relative to negative emotional stimuli in emotional goal-directed behaviour assessed by the emotional go/nogo task. This was evidenced by the psilocybin-induced increase in reaction times to negative and compared to positive stimuli, which is indicative of a relative positive emotional bias (Murphy et al., 1999; Feder et al., 2011). Furthermore, psilocybin augmented the sequential contextual influence of emotional stimuli in a manner that is consistent with a positive emotional bias. Specifically, psilocybin augmented the effect that sequential repetition of positive stimuli facilitates processing (Schulz et al., 2007; Thomas et al., 2009), which was indicated by a particularly strong decrease in the reaction times to repeated positive stimuli after psilocybin administration. This sequential facilitating effect was absent for repeated negative stimuli in all drug conditions. Repeated negative stimuli even increased the reaction times after psilocybin administration, which is indicative of an increased inhibition of negative concepts within the attentional (Joormann, 2004) or memory systems (Sass et al., 2011).

A possible psilocybin-induced positive bias in the attentional system is supported by the here revealed effect of psilocybin on event-related potentials in the emotional go/nogo task. Specifically, psilocybin strongly decreased the P300 component in all valence conditions, but most prominently for the negative and neutral stimuli. This valence-dependent P300 decrease was equally present in both the go and nogo condition, which suggests that this psilocybin-induced change in emotional processing is neither specific to response selection (go) nor inhibition (nogo), but rather, reflects a more general process underlying the P300 potential. For instance,

the P300 has previously been associated with the amount of attentional resource allocation (Polich, 2007), and several behavioural studies have previously demonstrated that psilocybin attenuates attentional performance (Gouzoulis-Mayfrank et al., 2002; Carter et al., 2005; Vollenweider et al., 2007; Quednow et al., 2011). Therefore, the strong psilocybin-induced decrease of the P300 that was revealed in all valence conditions may reflect an important electrophysiological index of the previously reported psilocybin-induced attentional deficits. Furthermore, the decrease was also valence-dependent, which suggests that psilocybin may attenuate the allocation of attentional resources to neutral and negative stimuli more strongly than to positive stimuli and therefore, produce a relative positive attentional bias.

Taken together, our results from self-report, behavioural and neurophysiological measurements demonstrate for the first time that psilocybin shifts emotional processing towards positive and away from negative information, an effect that is consistent across different psychological domains, including emotional face recognition, emotional goal-directed behaviour and mood states.

5.1.2 Visual processing

The analysis of the spatiotemporal dynamic of visual modal object completion provides important insights regarding the effect of psilocybin on the visual cortex response to external visual stimuli and the relationship of these effects to the formation of visual hallucinations. Specifically, we found that the early cortical response to visual stimuli, indexed by the P1 potential, was slightly increased by psilocybin over the medial occipital electrode sites, and the sLORETA analysis localised this increase to the early visual areas. The psilocybin-induced increase in the P1 amplitude may reflect an increase in perceived brightness, which has previously been shown to modulate the P1 potential response to Kanizsa figures (Proverbio and Zani, 2002) and is often reported after indolamine hallucinogen administration (Siegel and Jarvik, 1975).

In contrast to this initial increase in early visual cortex activity, we found that psilocybin dose-dependently decreased the N170 potential. The N170 potential is critical for object completion because Kanizsa figures evoke a higher N170 amplitude and underlying LOC and V2 activation compared with control figures (Murray et al., 2002; Murray et al., 2004; Spencer et al., 2004; Foxe et al., 2005; Murray et al., 2006; Seghier and Vuilleumier, 2006; Yoshino et al., 2006; Knebel and Murray, 2012). Psilocybin produced a more pronounced reduction of the N170 amplitude and activation of the LOC in response to Kanizsa figures compared with the non-Kanizsa figures, which indicates that psilocybin disrupts the neuronal processes of modal object completion. Because object completion is crucial for coherent visual perception (Lesher, 1995), and in particular, to delineate multiple objects from each other or their background (Stanley and Rubin, 2003; Yoshino et al., 2006), the disruption likely contributes to psilocybin-induced altered visual perceptual experiences.

Direct support for the view that the N170 potential modulation is associated with subjective perceptual alterations derives from the finding that the reported intensity of visual hallucinations and audiovisual synaesthesia correlated with decreases in the N170 amplitude in both the Kanizsa and non-Kanizsa conditions. Exploring the relationship between visual hallucinations and the N170 potential decrease in greater detail indicated that the psilocybin-induced reduction of the current source density in the right-lateralised LOC, V2 and posterior parietal areas correlated significantly with the intensity of visual hallucinations. This localisation is in line with the results of previous imaging studies reporting decreased extrastriate activation in response to external visual stimuli in patients with visual hallucinations compared with patients without hallucinations (Howard et al., 1995; Ffytche et al., 1998). Furthermore, we found that the activation was selectively decreased during the time course of the N170 potential. Decreased activation during this time period has previously been reported in studies investigating acoustic (Tiihonen et al., 1992; Hubl et al., 2007) and visual hallucinations (Spencer et al., 2004). Therefore, the decreased stimulus-induced activation in modality-specific cortical areas during the time course of the N1/N170 potential may be a characteristic of both acoustic and visual hallucinations.

During the post-N170 period, psilocybin strongly and dose-dependently reduced the P300 potential in the modal object completion task, an effect that was also revealed in the emotional goal-directed behaviour task (see Chapter 5.1.1). The attenuation of the P300 potential in the modal object completion task may be fostered by a psilocybin-induced disruption of the shift from occipital to parietal processing because the microstate analyses revealed that the occipital electrophysiological configuration appearing at the beginning of the P300 potential time period was prolonged by psilocybin, whereas the later parietal configuration was shortened by psilocybin.

Psilocybin, however, not only modulated the visual cortex response to external visual stimuli, as indicated by the analysis of the spatiotemporal dynamic of visual modal object completion, but further strongly affected the pre- and poststimulus alpha oscillations. Specifically, psilocybin differentially influenced the alpha power during the pre- and poststimulus time-range. During the prestimulus time-range psilocybin strongly decreased the high level of parieto-occipital alpha power that was observed in the placebo condition. Parieto-occipital alpha power inhibits the excitability of the visual network (Foxe et al., 1998; Thut et al., 2006; Klimesch et al., 2007; Romei et al., 2008a; Romei et al., 2008b; Jensen and Mazaheri, 2010; Klimesch, 2011; Mathewson et al., 2011), and therefore, the psilocybin-induced decrease in the prestimulus alpha power may reflect a disinhibition that increases the excitability state of the visual cortex in the absence of direct stimulus-driven processing. In contrast to this prestimulus increase in excitability, psilocybin blocked the stimulus-induced decrease in alpha power (i.e., blocked “alpha desynchronization”) 200–400 ms poststimulus, which indicates that psilocybin decreases the stimulus-driven excitation.

This opposite effect of psilocybin on the excitability during the presence and absence of direct stimulus-driven processing suggests that psilocybin induces a processing mode, in which spontaneously self-organised patterns of neuronal excitation overwhelm the visual stimulus-driven neuronal excitation. Thus psilocybin seems to disrupt the normal processing mode, in which spontaneously patterned neuronal activity is inhibited to keep the perceptual consequences subliminal (Ermentrout and Cowan, 1979; Bressloff et al., 2001, 2002; Billock and Tsou, 2007; Rule et al., 2011; Butler et al., 2012). According to computational models, an increase in spontaneous neuronal activity promotes the formation of elementary visual hallucinations (Ermentrout and Cowan, 1979; Bressloff et al., 2001, 2002; Billock and Tsou, 2007; Butler et al., 2012), which are phenomenologically similar to the elementary visual hallucinations that are produced by classical hallucinogens (Klüver, 1966; Siegel and Jarvik, 1975). Psilocybin induced elementary hallucinations and decreased inhibition by decreasing the alpha power in almost all of the subjects, which suggests that these alpha effects may be implicated in the formation of visual hallucinations. However, the correlation between the psilocybin-induced decrease in alpha oscillations and the subject-reported intensity of visual hallucinations did not reach statistical significance, indicating that the alpha power decrease may not be sufficient to generate subjectively experienced visual hallucinations.

Together these results show for the first time the various effects of psilocybin on the neurophysiological processes of visual perceptions in human subjects. These effects include a decrease of prestimulus parieto-occipital alpha activity that results in an increased prestimulus excitability state of the visual pathway. Although this psilocybin-induced increase in prestimulus excitability may contributed to augment the initial visual cortex response to visual stimuli that is indexed by the increased medial P1 potential (discussed in detail in Chapter 4), later stages in the processing of visual stimuli seems to be generally disrupted by psilocybin because psilocybin decreased the N170, the P300 potential and the stimulus-induced alpha-desynchronization.

5.2 The role of serotonin subreceptors in emotional and visual processing

5.2.1 Emotional processing

Although the psilocybin-induced state is consistently characterised by a bias towards positive compared to negative emotional states across different psychological domains, we revealed that different serotonin subreceptors mediate the psilocybin-induced emotional effects.

Activation of the 5-HT2A receptors is responsible for the psilocybin-induced positive mood states, indicated by the finding that the psilocybin-induced increase in the scores of the positive mood subscales of the PANAS and the 5D-ASC questionnaires was blocked by the preferential 5-HT2A antagonist ketanserin. These strong mood-enhancing effects of 5-HT2A receptor activation contrast with the usually absent acute mood effects of drugs that modulate the serotonergic tone such as acute tryptophan depletion (Hayward et al., 2005; Robinson and Sahakian, 2009; Roiser et al., 2009) or selective serotonin reuptake inhibitor (SSRI) administration (Harmer et al., 2003; Bhagwagar et al., 2004; Harmer et al., 2008). This apparent disparity suggests that 5-HT2A is much more closely linked to mood state than the serotonergic tone.

In addition, 5-HT2A receptors appear to be crucially implicated in the recognition of negative facial expressions because ketanserin blocked the psilocybin-induced attenuation in recognising negative emotional states from the eye region of human faces. This finding is in line with the central role of serotonin in emotional facial recognition, as previously established by pharmacological (Harmer et al., 2003; Bhagwagar et al., 2004; Hayward et al., 2005; Bedi et al., 2010; Victor et al., 2010) and genetic studies (Hariri and Holmes, 2006), but it extends this notion by showing that specific activation of 5-HT2A receptors likely biases facial recognition away from negative emotion.

In contrast to the crucial contribution of 5-HT2A receptors to modulating mood states and emotional face recognition, the psilocybin-induced effects on the emotional processing bias in the go/nogo task were not blocked by pretreatment with ketanserin. Thus, the psilocybin-induced emotional bias might be due to the stimulation of 5-HT1A or 5-HT2C receptors instead of 5-HT2A receptors. However, the strong valence-independent reduction of the P300 observed after psilocybin administration was partially reversed by ketanserin, indicating an involvement of 5-HT2A receptors in the valence-independent attentional performance.

These findings provide the first evidence for the effects of 5-HT2A receptor activation on emotional processing in different psychological domains. In particular, a crucial role for 5-HT2A receptor activation in enhancing mood states and in disrupting the recognition of negative facial expressions was identified. These results demonstrate the feasibility of using psilocybin in

combination with ketanserin to further elucidate the role of 5-HT2A receptor in emotional processing.

5.2.2 Visual processing

Serotonin 2A receptors strongly contribute to the effects of psilocybin on the P1 and N170 visual-evoked potentials. Specifically, the preferential 5-HT2A antagonist ketanserin blocked the psilocybin-induced decrease of the N170 potential and the associated psilocybin-induced visual hallucinations and audio-visual synaesthesia. These findings not only support the idea that 5-HT2A rather than 5-HT1A receptor stimulation is the key mechanism for the generation of visual hallucinations (Vollenweider et al., 1998) and audiovisual synaesthesia, but further suggest that the decrease in the N170 potential is a crucial mechanism that underlies the 5-HT2A receptor-mediated subjective visual perceptual alterations.

Furthermore, an opposing influence of 5-HT2A agonism and antagonism on the P1 potential is indicated by the finding that the preferential 5-HT2A antagonist ketanserin decreased the P1 potential over the same medial electrode sites, where psilocybin increased the P1 potential. The P1 increase by psilocybin was linked to the modulations of the prestimulus alpha power (see above), whereas the decrease of the P1 potential by ketanserin was associated with a concomitant decrease in alpha phase locking. The latter finding supports the notion that alpha phase locking and the P1 potential are closely associated (Gruber et al., 2005; Fellinger et al., 2011; Klimesch, 2011), and that the attenuation of the P1 potential may be driven by a 5-HT2A receptor antagonism-induced disruption of alpha phase resetting.

In addition, a crucial contribution of 5-HT2A receptor activation to the mediation of the psilocybin-induced effects on the alpha power was revealed in our study by the finding that the preferential 5-HT2A antagonist ketanserin blocked the pre- and poststimulus effects of psilocybin on the alpha power. This strong effect of 5-HT2A receptor activation on alpha power is consistent with the known anatomical and functional properties of 5-HT2A receptors in the visual cortex of animals. The 5-HT2A receptors in the visual cortex are primarily expressed in layers 4–6 (Watakabe et al., 2009; Moreau et al., 2010), which are crucially implicated in the generation of alpha rhythms (Steriade et al., 1990; Lopes da Silva, 1991; Silva et al., 1991; Jones et al., 2000; Pinto et al., 2003; Bollimunta et al., 2008; Sun and Dan, 2009; Bollimunta et al., 2011; Buffalo et al., 2011). Furthermore, the activation of 5-HT2A receptors in the visual cortex alters the excitatory-inhibitory balance in favour of excitation of pyramidal neurons in layer 5 (Moreau et al., 2010). Excitatory synaptic inputs in layer V modulate alpha oscillations (Jones et al., 2000; Karameh et al., 2006; Sun and Dan, 2009), which suggests that the 5-HT2A receptor-induced excitatory effects are closely associated with alpha oscillations. Furthermore, assuming that the presentation of external stimuli predominantly increases the firing rate of visual neurons from

the prestimulus level (Quiroga et al., 2005; Montemurro et al., 2008), the opposite effects of 5-HT2A receptor stimulation on the pre- and poststimulus alpha power are consistent with the suppressive effect of 5-HT2A receptor activation on visual neurons with high firing rates, and the facilitating effect on neurons with low firing rates (Watakabe et al., 2009).

Taken together, we revealed several 5-HT2A dependent neurophysiological mechanisms underlying visual processing. Out of these mechanisms, the decrease of the N170 potential by 5-HT2A receptor activation was most closely associated with visual hallucinations, indicating that the decrease might a crucial mechanism of 5-HT2A receptor mediated visual hallucinations.

5.3 Implications for psychiatric disorders

5.3.1 Implications for mood disorders

Psilocybin produced in our emotional study behavioural and electrophysiological emotional effects that were opposite to the dysfunctional emotional processing bias observed in depressed subjects in emotional facial recognition (Bhagwagar et al., 2004; Hayward et al., 2005; Joormann and Gotlib, 2006; Victor et al., 2010), goal-directed behaviour (Murphy et al., 1999; Erickson et al., 2005; Krompinger and Simons, 2009) and mood states (Lovejoy and Steuerwald, 1995; Peeters et al., 2003). In emotional facial recognition, psilocybin selectively disrupts the recognition of negative facial expressions, whereas depressed subjects have lower recognition rates for positive compared with negative expressions (Bhagwagar et al., 2004; Hayward et al., 2005; Joormann and Gotlib, 2006; Victor et al., 2010). In the emotional go/nogo task psilocybin increased the reaction times and decreased the P300 amplitudes, particularly for negative and neutral stimuli, while depressed subjects were delayed in responding to positive cues (Murphy et al., 1999; Erickson et al., 2005) and displayed an increased P300 component for negative stimuli (Krompinger and Simons, 2009). Finally, depressed subjects have decreased positive affect scores in the PANAS (Lovejoy and Steuerwald, 1995; Peeters et al., 2003), and in contrast psilocybin selectively increases positive affect scores in the PANAS.

Thus, this contrasting pattern suggests that psilocybin has the potential to acutely shift the negative emotional processing biases in depressive patients towards positive emotions. This shift supports the putative antidepressant potential of psilocybin (Vollenweider and Kometer, 2010; Grob et al., 2011) because a shift in the emotional processing bias is implicated in therapeutic effects of SSRIs (Harmer, 2008), and cognitive behavioural therapy (Disner et al., 2011). This acute psilocybin-induced shift may result in a sustained positive bias through psilocybin-induced neuroplastic effects (Vollenweider and Kometer, 2010) or through psychological relearning processes that are associated with a shift in the emotional processing bias (Harmer et al., 2009; Pringle et al., 2011; Sharp and Cowen, 2011).

Specifically, indolamine hallucinogens such as psilocybin induce several neuroplastic effects, including, for instance, a temporary downregulation of 5-HT2A receptor density (Buckholtz et al., 1990), the induction of BDNF (Vaidya et al., 1997; Cavus and Duman, 2003) and an alteration of the spine morphology of prefrontal cortical neurons (Jones et al., 2009). Because the current study revealed that the acute shifts in mood state and emotional face recognition are mediated by 5-HT2A receptor activation, it is conceivable that these neuroplastic effects involve the modulation of 5-HT2A receptor density or signalling.

From a psychological perspective, an acute shift in the emotional processing bias could foster the relearning of new positive emotional associations brought about by the exposure to social

and emotional stimuli. Subsequently, this might lead to an improvement in depressive symptoms because new, positive emotional contingencies are experienced (Harmer et al., 2009; Pringle et al., 2011; Sharp and Cowen, 2011). Taken together, a possible mechanism underlying the antidepressant effect of psilocybin may be an acute psilocybin-induced shift in the emotional bias that leads in conjunction with neuroplastic effects and psychological relearning processes to an improvement in depressive symptoms.

Furthermore, the revealed contributions of the serotonin 2A receptor to the psilocybin-induced positive processing bias have implications for the mechanisms underlying the pathophysiology and serotonergic treatments of dysfunctional emotional biases. Specifically, agonistic action at the 5-HT2A receptors was identified in the current thesis as a mechanism for shifting emotional facial recognition and mood states towards positive emotions. A disruption in this mechanism may be implicated in the repeatedly observed dysfunctional emotional processing biases in facial recognition and mood state in depression because depressed subjects often have altered density of 5-HT2A receptors (Meyer et al., 1999; Meyer et al., 2001; Bhagwagar et al., 2006; Shelton et al., 2009). Furthermore, this mechanism might even underlie the therapeutic action of SSRIs because chronic administration of SSRIs to depressed patients not only shifts negative mood states and negative bias in facial recognition (Burghardt et al., 2004; Victor et al., 2010) but also seems to normalise the alterations in 5-HT2A receptor densities (Meyer et al., 2001; Yamauchi et al., 2006).

5.3.2 Implications for schizophrenia and Parkinson's disease

We identified several key neurophysiological mechanisms that underlie 5-HT2A agonist-induced alterations in visual processing. These mechanisms could also underlie the visual disturbances and hallucinations observed in Parkinson's disease and schizophrenia patients because increased 5-HT2A receptor densities have been found in these psychiatric disorders and have been associated with visual hallucinations (González-Maeso et al., 2008; Ballanger et al., 2010; Huot et al., 2010).

In particular, we identified reduced extrastriate visual cortex activation during the time course of the N170 potential as a potential key mechanism of 5-HT2A agonist-induced visual hallucinations. This mechanism may also be implicated in the pathophysiology of visual hallucinations in Parkinson's patients because patients with visual hallucinations showed stronger reductions in extrastriate cortex activation to visual stimuli (Meppelink et al., 2009) and more pronounced impairments in visual object recognition (Meppelink et al., 2008; Koerts et al., 2010) than patients without hallucinations. Similarly, an attenuated N170 potential in response to Kanizsa- and non-Kanizsa figures has also been observed in schizophrenia patients, and it was found to be most prominent in patients with visual hallucinations (Spencer et al., 2004), supporting the

idea that a 5-HT2A receptor-mediated decrease in the N170 may also underlie visual hallucinations in schizophrenia patients. However, it is noteworthy that two other previous studies using Kanizsa figures in schizophrenia patients reported either no reduction (Foxe et al., 2005) or only a trend towards a reduction (Spencer et al., 2003). A possible reason for the inconsistency in the findings regarding the N170 potential may be the fact that only approximately 30% of schizophrenia patients typically report visual hallucinations (Bracha et al., 1989). This subgroup of patients with hallucinations has increased cortical expression of 5-HT2A receptors (González-Maeso et al., 2008) and a more pronounced attenuation of the N170 potential (Spencer et al., 2004). Therefore, it is conceivable that dysfunction of the 5-HT2A receptor and the associated decrease of the N170 potential may be a pathophysiological mechanism in a subgroup of schizophrenic patients with visual hallucinations.

5.4 Future research questions

5.4.1 Generalisation and specification of the psilocybin-induced emotional processing bias

The current thesis revealed a psilocybin-induced shift in the emotional processing bias, an effect that was consistent over different emotional domains. Therefore, the psilocybin-induced shift in emotional processing bias may be generalisable to other psychological dimensions such as the consolidation and retrieval of emotional memory, the formation of self-referential schemas, expectations and decision-making, which should be tested in further studies

Moreover, the results of the emotional go/nogo task suggested that psilocybin induced a positive attentional bias. However, whether an increase in the endogenous allocation of attentional resources to positive stimuli or an increase in the stimulus-driven (external) attention to positive stimuli underlies this psilocybin-induced positive bias, remains to be determined. To elucidate this issue further, we began to assess in 15 healthy subjects the influence of psilocybin and ketanserin on the extend that visual processing is modulated by endogenous attention to external stimuli, by the salience of external stimuli or by the interaction between these variables. To simultaneously manipulate these factors, two vertical and two horizontal stimuli were presented together, which were all emotional, all neutral or a combination of both (manipulation of emotional salience). Additionally, the subjects were instructed to either look at the horizontal or vertical stimuli (manipulation of endogenous allocation of attentional resources). These two manipulations were independent, which allowed the experimental assessment of the interaction between emotional salience and endogenous attention. To quantify visual processing as a function of these manipulations, we used an experimental design called frequency tagging, which has previously been used to isolate the neuronal response to simultaneously presented visual stimuli (Morgan et al., 1996; Müller et al., 1998; Ding et al., 2006). Specifically, the simultaneously presented stimuli flicker at different frequencies. The SSVEPs are elicited by the flicker, and therefore, have exactly the same frequency as the presented stimulus. Accordingly, the processing of the different stimuli can by assessed by a frequency analysis. A preliminary analysis of the results of this experiment in 8 subjects indicates that psilocybin generally increases the processing of positive stimuli, but in particularly when endogenous attention is directed to the stimuli.

5.4.2 Alpha, excitability and visual percepts

The effect of psilocybin on the relationships between visual percepts, excitability and alpha oscillations can be explored further with a combination of the TMS and EEG methods. For instance, the threshold for TMS-induced phosphene, which is the intensity level at which phosphenes are perceived, is a reliable marker for the excitability of the visual cortex (Kammer et al., 2001; Gothe

et al., 2002). This threshold has been shown to be inversely related to the alpha power (Romei et al., 2008b; Romei et al., 2010) and to be reduced in conditions that have an increased prevalence for visual hallucinations, such as migraine (Gerwig et al., 2005), light deprivation (Boroojerdi et al., 2000), pregeniculate blindness (Gothe et al., 2002) or Lewy body dementia (Taylor et al., 2011). Accordingly, assessing the influence of psilocybin on the threshold of TMS-induced phosphene and relating this threshold to the appearance of visual hallucinations and alpha power may be helpful for further elucidating the exact causal relationships between excitability, alpha power and the formation of visual hallucinations in hallucinogen-induced states.

Furthermore, the 5-HT2A receptor-mediated decrease of the alpha power may not only lead to perceptual consequences of spontaneous, self-organised excitation patterns, as discussed above, but may also result in increased distractibility or working memory impairments. Specifically, the alpha power gates sensory input by inhibition (van Dijk et al., 2008; Rajagovindan and Ding, 2011), and therefore, is crucial for reducing interference with new sensory input during working memory maintenance (van Dijk et al., 2008; Haegens et al., 2012). Therefore, it is conceivable that the psilocybin-induced impairment in modulating alpha power revealed here contributes to the previously observed psilocybin-induced increase in distractibility (Carter et al., 2005), working memory impairments (Wittmann et al., 2007) and attentional control deficits (Quednow et al., 2011), which should be tested in further experiments.

5.4.3 Alpha power and emotions

Several approaches from the visual and emotional experiments could be combined in further studies to reveal, for instance, the role of the alpha power in the anticipation of emotional stimuli. The anticipation of a visual stimulus gradually decreases the parieto-occipital alpha power immediately before stimulus presentation (Ergenoglu et al., 2004; Rohenkohl and Nobre, 2011; Stokes et al., 2012), which is thought to reflect an adaptation of the excitability level for optimal stimulus processing. The anticipatory processes are modulated by the emotional valence of a forthcoming stimulus (Bermpohl et al., 2006; Herwig et al., 2007). Therefore, it would be interesting to test whether the anticipation of a positive, negative or neutral visual stimulus may differentially modulate the alpha power immediately before stimulus presentation.

5.5 References

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